Published in final edited form as:

Curr Eye Res. 2008 November ; 33(11): 946–953. doi:10.1080/02713680802447121.

Effect of Daily Prolonged Ketamine Anesthesia on Intraocular Pressure in Monkeys

Theodora J. Bunch, BS¹, Baohe Tian, MD¹, Jennifer L. Seeman, DVM¹, B'Ann T. Gabelt, MS¹, Ting-Li Lin, MS², and Paul L. Kaufman, MD¹

¹Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, WI, USA

²Department of Statistics, University of Wisconsin, Madison, WI, USA

Abstract

Purpose—To determine if repeated intramuscular ketamine in monkeys on consecutive days affects intraocular pressure (IOP), and if the ketamine-induced IOP change has any relationship to systemic dehydration and/or changes in mean arterial pressure (MAP) of the animals.

Methods—Nine monkeys were studied per 4 protocols. IOP was determined hourly for 6-hrs by Goldmann tonometry under ketamine anesthesia on 3 (protocol 1) or 5 (protocols 2 and 3) consecutive days, or on alternating days 1, 3 and 5 (protocol 4). Monkeys in protocols 3 and 4, but not in protocols 1 and 2, received subcutaneous Ringer's fluids at the end of each 6-hr session on days 1-4 or 1, 3 and 5; monkeys in protocols 2 and 3 received intravenous fluid infusion throughout the experiment on day 5. In protocols 2-4, MAP was measured hourly following each IOP measurement.

Results—Monkeys receiving ketamine but no Ringer's fluids in protocol 1 or 2 showed significant IOP declines on days 2-3 or 2-4. The IOP declines were greater in magnitude in protocol 1 than in protocol 2. Daily subcutaneous Ringer's fluids appeared to delay IOP declines in protocol 3. Continuous intravenous fluid infusion on day 5 variably prevented IOP declines in protocols 2 and 3. Monkeys receiving ketamine and subcutaneous fluids on alternate days in protocol 4 showed no decline in IOP. No significant relationship between IOP and MAP was observed.

Conclusions—Anesthesia induced by repeated intramuscular ketamine on consecutive days may produce significant IOP declines. Systemic dehydration during the anesthesia seems to be the predominant factor contributing to the IOP reduction. However, inter-individual differences in monkeys indicate that multiple factors may be involved. This study also suggests that fluid supplementation plus alternating anesthesia with recovery days may prevent IOP reduction in monkeys resulting from daily-prolonged ketamine anesthesia.

Keywords

dehydration; intraocular pressure; ketamine anesthesia; mean arterial pressure; monkey eye

Introduction

Ketamine is a rapid-acting general anesthetic that has dissociative, analgesic and psychedelic properties. Ketamine has a complex mechanism of action that is further complicated by stereoselectivity; however, antagonism of glutamate NDMA receptors is thought to underlie

Correspondence: Paul L. Kaufman, MD. Department of Ophthalmology & Visual Sciences, University of Wisconsin School of Medicine and Public Health 3310 University Ave, Ste 206, Madison WI 53705-2135. Tel: 608-263-6074, Fax: 608-263-1466, E-mail: kaufmanp@mhuh.ophth.wisc.edu.

its analgesic, dissociative and neuroprotective effects.¹ Ketamine has been widely used as the anesthetic to measure intraocular pressure (IOP) during ocular examinations in children and IOP experiments with different species of animals. The possible effect of ketamine on IOP has been controversial. In ocular examinations under anesthesia in children, some studies report that ketamine elevates IOP,^{2,3} some suggest that the impact of ketamine on IOP is comparatively modest,⁴ and others show that ketamine decreases IOP.^{5,6} In IOP experiments with animals, ketamine increases IOP in dogs, rabbits and cats,⁷⁻⁹ but decreases IOP in rats.¹⁰ For non-human primates, however, most studies show that ketamine does not significantly affect IOP.¹¹⁻¹³

Ketamine is the first choice as the anesthetic in monkey IOP experiments. In addition to several advantages such as rapid onset and recovery, intact pharyngeal-laryngeal reflexes, low incidence of respiratory depression, and wide range of safe doses, the most important reason for ketamine being selected for this purpose is that, unlike other anesthetics,^{11,14} ketamine does not substantially lower IOP.¹¹⁻¹³ Having a physiologically normal and stable IOP is particularly advantageous when studying potential ocular hypotensive agents, because IOP responses to experimental agents may be more easily detected in eyes with higher and stable baseline IOPs. Although IOP measurements in monkeys under conscious conditions (e.g., by using restraint techniques) may avoid possible anesthetic-induced IOP reduction, animal stress induced by the restraint technique and the stress-induced muscle tension or increased blood pressure may artificially elevate IOP,¹² which could affect IOP results. Additionally, it is difficult and time-consuming to train the animals. Therefore, ketamine anesthesia is still a common option for IOP experiments in non-human primates.

However, all previous conclusions about the effect of ketamine on IOP are based on studies lasting from several minutes to several hrs on a single day²⁻¹³. It is not clear how ketamine will affect IOP in prolonged multiple consecutive day experiments. This study has been undertaken to determine whether there are significant changes in IOP when non-human primates are sedated with ketamine for 6-7 hrs on 3 or 5 consecutive experimentation days. The results suggest there may be confounding effects of prolonged ketamine anesthesia on IOP responses to topical or intraocular drugs, which need to be taken into account in experimental design.

Materials and Methods

Animals and Anesthesia

Nine cynomolgus monkeys (*Macaca fascicularis*) of both sexes, 3-12 years of age, and weighing ~3 to 6 kg, were studied in various groupings per 4 protocols. Anesthesia was induced with intramuscular ketamine hydrochloride (Ketaject®; Phoenix Pharmaceutical, Inc. St. Joseph, MO; 10mg/kg initially [at ~8:30 AM], 5-10mg/kg supplementally as needed). Supplemental doses of ketamine, which are required in order to obtain good IOP measurements, may vary in different monkeys or in the same monkey on different occasions (see below). Monkeys were allowed to partially recover from the anesthesia in transfer cages in the laboratory during intervals throughout the experiment (usually sitting up before the next ketamine dosing) when IOP was not being measured. At the conclusion of each IOP experiment (at ~3:00 PM), monkeys were returned to cages in the Animal Care Unit after complete recovery from the anesthesia. Overnight between consecutive experimentation days, monkeys had accesses to food and water. In order to allow enough time for animals to eat between experiments, no pre-sedation fasting was conducted. Animals were fed with their usual amounts of foods following each experiment. The general impression from staff was that most of the food was consumed by the next morning. No animals were removed from the study for health reasons in all protocols. No physical behavior changes were observed during the study or shortly after the study. All investigations were in accordance with University of Wisconsin

and NIH guidelines for animal use, and with the ARVO Statement on the Use of Animals in Ophthalmic and Vision Research.

Experimental Protocols

Two different investigators (1 and 2) were responsible for administering anesthesia and taking IOP measurements for the various protocols (Protocol 1 was performed by Investigator 1 and protocols 2 to 4 were performed by Investigator 2). The 2 investigators chose different tear film indicators for IOP measurement as indicated below per their preferences. Since a given protocol was conducted in its entirety by a single investigator, the different tear film indicators should not affect the results (see the Discussion).

Protocol 1—The effect of consecutive daily prolonged ketamine anesthesia on IOP was determined in 3 monkeys (~3-6 kg, 6-12 yrs) by Investigator 1. IOP was measured hourly for 6 hrs (~9:00 AM -3:00 PM) on 3 consecutive days with a minified Goldmann applanation tonometer,¹⁵ using fluorescein as the tear film indicator, with the monkey lying prone in a head holder and the eyes positioned at 4 to 8 cm above the heart. No supplemental subcutaneous or intravenous fluid (see below) was administered at any time over the course of the 3-days of experiments.

Protocols 2, 3 and 4—To determine if systemic dehydration and changes in blood pressure were involved in the IOP decline during experiments on consecutive days, a different group of 6 monkeys (~3-4 kg, 3-8 yrs) was studied by Investigator 2 per three protocols (protocols 2, 3 and 4). IOP was measured as in protocol 1, but “Half and Half®” creamer solution (Borden Inc., Columbus, OH) was used as the tear film indicator.¹⁶ In protocols 2 and 3, monkeys (n=3 for each protocol) underwent IOP measurements on 5 consecutive days. Following each IOP measurement, mean arterial pressure (MAP) was measured by a brachial cuff with an automatic blood pressure monitor (Dinamap Pro 100 Research monitor, Critikon, Tampa, FL). On days 1 to 4, at the end of each 6-hr session, approximately 60 ml of supplemental fluid (lactated Ringer's fluid with 5% dextrose; Baxter Healthcare Co., Deerfield, IL) was administered subcutaneously to monkeys in protocol 3, but not in protocol 2. On day 5, the effect of constant intravenous fluid infusion (~10ml/kg/hr) on IOP was determined in monkeys in both protocols 2 and 3. In protocol 4, all 6 monkeys used in protocols 2 and 3 were studied again after a recovery period of several weeks or more. Ketamine administration, IOP measurements and MAP measurements were conducted on alternating days 1, 3 and 5 in the same manner as described in protocols 2 and 3. At the end of each experimental day, each monkey received a bolus subcutaneous injection of fluid (~6 ml/kg).

Statistical Analysis

To increase statistical power of the data generated from small samples with repeated measurements, the data were analyzed as a whole using general linear regression models, analysis of covariance (ANCOVA) and analysis of variance (ANOVA). Correlations among repeated measurements were modeled using generalized estimating equations (GEEs). Pairwise comparisons between baseline values (hr 0) on different days were performed, and corresponding p-values were adjusted using the Tukey's method. Specific analyses are described as follows:

IOPs of both eyes of each monkey were averaged as one sample. Mean IOP was derived from average IOPs of both eyes of all individual animals. For each protocol, general linear regression models with repeated measurements were used to obtain slopes of mean IOP declines on different days. Comparisons between the slope and zero on each day and between the slopes on different days were performed using t-test and contrast based on the fitted models respectively. MAP comparisons between hr 0 and hr 6 on different days were made using

ANCOVA with repeated measurements. Initial IOP or MAP (hr 0) comparisons between experimentation days were analyzed using ANOVA. Relationship between IOP and MAP was analyzed using general linear regression models. Ketamine dosage comparisons between experimentation days in each protocol and between protocols on different days were analyzed using ANOVA. All analyses were performed using SAS v9.1.3.

Results

IOP

Protocol 1 (Figure 1)—The initial mean IOP (the mean IOP at hr 0 [~9:00AM for all protocols]) did not change from day 1 to day 2, but tended to decrease slightly from day 2 to day 3. On each day, IOP tended to decrease over time. Mean slopes of the IOP declines on days 2 and 3 were significantly different from 0. The absolute value of the day-3 slope tended to be greater than that of day 1 or day 2.

Protocol 2 (Figure 2)—The initial mean IOP was essentially stable from day 1 to day 3, but tended to decrease slightly from day 3 to day 5. On days 2 to 4, mean IOPs slightly decreased over time. Mean slopes of the IOP declines were significantly different from 0 on days 2 to 4. The slope on day 2 was significantly different from that on day 1, indicating that IOP tended to decrease. The mean slope changed from significantly less than zero on day 4 to slightly greater than zero on day 5, suggesting that intravenous fluid infusion throughout the experiment prevented the IOP decline during ketamine anesthesia.

Protocol 3 (Figure 3)—The initial mean IOP was not significantly different from day 1 to day 5. On days 2 to 4, mean IOPs slightly and variably decreased over time. The mean slope of the IOP decline on day 4 was significantly different from 0. However, the slope on day 5 was less significant than that on day 4, suggesting that intravenous fluid infusion throughout the experiment on day 5 may have partially prevented the IOP decline during ketamine anesthesia.

Protocol 4 (Figure 4)—The initial mean IOP was not significantly different on days 1, 3 or 5. On the 3 days, mean IOPs were essentially unchanged over time. Mean slopes of the IOPs on all days were approximately equal to zero and were not different from each other, indicating that subcutaneous fluid supplementation plus one-day of recovery between experimentation days prevented the IOP decline during ketamine anesthesia.

Ketamine Dosing

Ketamine doses (mg/kg/day) on different days for each protocol are shown in Table 1. For days 1-3, the ketamine dose on each day in protocol 2 was variably lower than that in protocol 1 or protocol 3, in which the difference between protocols 1 and 2 on days 2 and 3 and that between protocols 2 and 3 on day 3 were statistically significant. Ketamine dosing on day 4 was slightly but significantly higher than that on day 3 in protocol 2 or on day 1 in protocol 3; ketamine dosing on day 5 was significantly higher than that on days 1 to 4 in protocol 2 or 3. Additionally, the ketamine dose on day 5 in protocol 3 was significantly higher than that in protocol 2. The substantially higher doses of ketamine on day 5 in protocols 2 and 3 were required to keep the animals asleep while receiving intravenous fluid infusion and to prevent the animals from dislodging the intravenous infusion lines. Since drug accumulation or distribution is not only related to body weight, but also to drug clearance,¹⁷ the average ketamine dose per monkey per day was also compared between protocols (Table 1). The dose in protocol 2 was significantly lower than that in protocol 1 or protocol 4, but not less than that in protocol 3 (day 5 was excluded from the calculation of the average ketamine dose per monkey per day for protocols 2 and 3).

MAP

Baseline MAP was slightly variable on different days for each protocol (76.11±4.92 – 97.33 ±6.01 mmHg in protocol 2; 74.22±2.00 – 93.22±8.62 mmHg in protocol 3; 86.56±5.69 – 94.17 ±5.21 mmHg in protocol 4). These changes were not significant except for a slight but significant increase on day 5 compared to that on day 3 (+26±3%) or 4 (+28±4%) in protocol 2. MAP at hr 6 was not significantly changed from baseline on any day in any protocol. No relationship between MAP and IOP was observed (data not shown).

Discussion

Although it is generally believed that ketamine does not substantially reduce IOP in monkeys, ¹¹⁻¹³ previous studies had often shown a tendency toward IOP reduction in the drug-free eye of ketamine-anesthetized monkeys during one-day experiments.^{18,19} In the present study, monkeys in protocol 1, which did not receive fluid supplements at any time, had significant reductions in IOP during ketamine anesthesia on 3 consecutive experimentation days (Figure 1). The IOP declines tended to increase in magnitude on each subsequent day of ketamine anesthesia, indicating that they are not likely attributable to diurnal IOP fluctuations. However, monkeys in protocol 2, which did not receive any fluid supplements during days 1 to 4, only showed small IOP reductions on days 2 to 4 (Figure 2). Causes for the difference between protocol 1 and protocol 2 are not clear. Although the two protocols were conducted by two different investigators, during which two different tear film indicators were used (fluorescein in protocol 1 and creamer in protocol 2), the IOP reductions were based on IOP changes from baselines within each protocol. Therefore, possible variances between investigators and/or between tear film indicators¹⁶ are probably not relevant to the results.

In order to obtain good IOP measurements, some monkeys require more ketamine than others or a given monkey may need different doses of ketamine on different occasions. In the current experiments, the ketamine dose per body weight per day was significantly higher in protocol 1 than in protocol 2 on days 2 and 3; the average ketamine dose per monkey per day was also significantly greater in the former than in the latter (Table 1). Therefore, the higher dosage of ketamine used in protocol 1 may have contributed to the substantial IOP reductions.

Although it is unknown how ketamine directly affects IOP, several indirect mechanisms might be involved in the IOP reduction during the daily-prolonged ketamine anesthesia. First, ketamine may decrease IOP by inducing muscle relaxation. Secondly, ketamine may dampen the animal's appetite and decrease their food and water intakes, and in turn induce weight loss and/or systemic dehydration. The latter may induce IOP reductions. In the present study, a slight and insignificant weight loss was observed in monkeys of protocols 2 and 3 that were weighed everyday during the study (data not shown), indicating that ketamine might dampen the animal's appetite. Although the weight loss was not significantly related to the change in baseline IOP, the systemic dehydration may not be excluded from the factors inducing IOP reduction during consecutive experimentation days (see below). Since different monkeys may respond to ketamine differently, changes in IOP after ketamine may be different in different groups of animals. For example, some monkeys may exhibit complete and stable muscle relaxation after ketamine (e.g., the monkeys in protocol 1), and others may not. The lack of muscle relaxation may not be improved by additional doses of ketamine in some monkeys. It is possible that IOP could be lower in monkeys exhibiting complete muscle relaxation compared to those that do not. Additionally, differences between monkeys in appetite after ketamine and/or eating or drinking habits overnight following the experiment may contribute to differences in weight loss and/or dehydration, and perhaps different IOP reductions. Nevertheless, although the magnitudes of IOP reductions are different between protocol 1 and protocol 2, both protocols show that anesthesia with ketamine on consecutive experimentation days does reduce IOP.

To determine if systemic dehydration was the cause of the IOP reductions, protocol 3 was conducted, during which subcutaneous fluid supplements were administered at the end of each 6-hrs of tonometry on days 1 - 4. Unlike in protocols 1 and 2, in which significant IOP declines began on day 2, the significant IOP decline was delayed until day 4 in protocol 3. This suggests that the subcutaneous fluid supplementation might have delayed the IOP reduction in protocol 3 (Figures 1-3). Additionally, the constant intravenous fluid infusion on day 5 in protocols 2 and 3 either prevented or attenuated the IOP decline (Figures 2 and 3), indicating that systemic dehydration may be involved in the IOP reduction before day 5 in these protocols. Since the ketamine dose used on day 5 in protocol 3 was doubled compared to that in protocol 2 (Table 1), the incomplete reversal of the IOP reduction during the intravenous fluid infusion on day 5 in protocol 3 suggests that high doses of ketamine may reduce IOP in monkeys by mechanisms other than dehydration during daily-prolonged anesthesia.

During IOP experiments on days 2 to 4 in protocols 2 and 3, MAP was not significantly altered and was unrelated to IOP. This is not contradictory to the hypothesis that the ketamine-induced IOP reduction may be due to systemic dehydration, because systemic dehydration may not necessarily decrease MAP.²⁰ However, since MAP was not measured in protocol 1 in which the magnitudes of IOP reductions were substantial, further studies are needed to clarify this issue.

It is worth noting that monkeys in protocol 4, which received similar ketamine doses to those in protocol 1, did not show any IOP reduction on any day (Figure 4). This suggests that a daily bolus subcutaneous fluid supplementation plus one-day of recovery between experimentation days, as conducted in protocol 4, may prevent IOP reductions during long-term IOP experiments in ketamine-anesthetized monkeys. This should be taken into account when designing protocols for long-term IOP experiments in monkeys under ketamine anesthesia. However, systemic dehydration after ketamine is not the only factor inducing IOP reduction, and other ketamine-relevant factors should also be considered when designing protocols. As described above, different responses to ketamine between monkeys and in the same monkey on different occasions are also important factors affecting IOP. Additionally, since previous studies of conscious monkeys have shown IOP reduction in the drug-free eye on some occasions,^{21,22} possible ketamine-irrelevant factors may also be involved. To minimize confounding factors (ketamine-relevant or not) in IOP studies with ketamine-anesthetized monkeys, it is very important to compare IOPs between opposite eyes of the same monkey on the same occasion.

Acknowledgements

This work was supported by grants from the U.S. National Eye Institute (R01 EY02698 and P30 EY016665), Research to Prevent Blindness and the Ocular Physiology Research and Education Foundation.

References

1. Wolff K, Winstock AR. Ketamine: from medicine to misuse. *CNS Drugs* 2006;20:199–218. [PubMed: 16529526]
2. Yoshikawa K, Murai Y. The effect of ketamine on intraocular pressure in children. *Anesth Analg* 1971;50:199–202. [PubMed: 5102632]
3. Nagdeve NG, Yaddanapudi S, Pandav SS. The effect of different doses of ketamine on intraocular pressure in anesthetized children. *J Pediatr Ophthalmol Strabismus* 2006;43:219–223. [PubMed: 16915900]
4. Peuler M, Glass DD, Arens JF. Ketamine and intraocular pressure. *Anesthesiology* 1975;43:575–578. [PubMed: 1190527]
5. Ausinsch B, Rayburn RL, Munson ES, Levy NS. Ketamine and intraocular pressure in children. *Anesth Analg* 1976;55:773–775. [PubMed: 1033690]

6. Blumberg D, Congdon N, Jampel H, et al. The effects of sevoflurane and ketamine on intraocular pressure in children during examination under anesthesia. *Am J Ophthalmol* 2007;143:494–499. [PubMed: 17317393]
7. Hofmeister EH, Mosunic CB, Torres BT, et al. Effects of ketamine, diazepam, and their combination on intraocular pressures in clinically normal dogs. *Am J Vet Res* 2006;67:1136–1139. [PubMed: 16817733]
8. Hahnenberger RW. Influence of various anesthetic drugs on the intraocular pressure of cats. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1976;199:179–186. [PubMed: 1083696]
9. Bar-Ilan A, Pessah NI. On the use of ketamine in ocular pharmacological studies. *J Ocul Pharmacol* 1986;2:335–344. [PubMed: 3503118]
10. Jia L, Cepurna WO, Johnson EC, Morrison JC. Effect of general anesthetics on IOP in rats with experimental aqueous outflow obstruction. *Invest Ophthalmol Vis Sci* 2000;41:3415–3419. [PubMed: 11006233]
11. Erickson-Lamy KA, Kaufman PL, McDermott ML, France NK. Comparative anesthetic effects on aqueous humor dynamics in the cynomolgus monkey. *Arch Ophthalmol* 1984;102:1815–1820. [PubMed: 6508621]
12. Bito LZ, Meritt SQ, DeRousseau CJ. Intraocular pressure of rhesus monkeys (*Macaca mulatta*) I. An initial survey of two free-breeding colonies. *Invest Ophthalmol Visual Sci* 1979;18:785–793. [PubMed: 110720]
13. Komaromy AM, Brooks DE, Kubilis PS, et al. Diurnal intraocular pressure curves in healthy rhesus macaques (*Macaca mulatta*) and rhesus macaques with normotensive and hypertensive primary open-angle glaucoma. *J Glaucoma* 1998;7:128–31. [PubMed: 9559500]
14. Mirakhur RK, Elliott P, Shepherd WF, McGalliard JN. Comparison of the effects of isoflurane and halothane on intraocular pressure. *Acta Anaesthesiol Scand* 1990;34:282–285. [PubMed: 2343729]
15. Kaufman PL, Davis GE. “Minified” Goldmann applanating prism for tonometry in monkeys and humans. *Arch Ophthalmol* 1980;98:542–546. [PubMed: 6767468]
16. Croft, MA.; Kiland, J.; Gange, SJ.; Aref, A.; Pelzek, CD.; Kaufman, PL. Comparison of Goldmann tonometry measurements using creamer vs fluorescein in cynomolgus monkeys. In: Lakshminarayanan, V., editor. *Basic and Clinical Applications of Vision Science*. Kluwer; Dordrecht: 1997. p. 213–216.
17. Casati A, Putzu M. Anesthesia in the obese patient: pharmacokinetic considerations. *J Clin Anesth* 2005;17:134–145. [PubMed: 15809132]
18. Gabelt BT, Robinson JC, Hubbard WC, Peterson CM, Debink N, Wadhwa A, Kaufman PL. Apraclonidine and brimonidine effects on anterior ocular and cardiovascular physiology in normal and sympathectomized monkeys. *Exp Eye Res* 1994;59:633–44. [PubMed: 7698258]
19. Tian B, Gabelt BT, Crosson CE, Kaufman PL. Effects of adenosine agonists on intraocular pressure and aqueous humor dynamics in cynomolgus monkeys. *Exp Eye Res* 1997;64:979–989. [PubMed: 9301479]
20. Fejes-Toth G, Naray-Fejes-Toth A, Ratge D. Evidence against role of antidiuretic hormone in support of blood pressure during dehydration. *Am J Physiol* 1985;249:H42–48. [PubMed: 2990241]
21. May JA, Chen H-H, Rusinko A, Lynch VM, Sharif NA, McLaughlin MA. A novel and selective 5-HT₂ receptor agonist with ocular hypotensive activity: (S)-(+)-1-(2-Aminopropyl)-8,9-dihydropyrano[3,2-e]indole. *J Med Chem* 2003;46:4188–4195. [PubMed: 12954071]
22. May JA, McLaughlin MA, Sharif NA, Hellberg MR, Dean TR. Evaluation of the ocular hypotensive response of serotonin 5-HT_{1a} and 5-HT₂ receptor ligands in conscious ocular hypertensive cynomolgus monkeys. *JPET* 2003;306:301–309.

Figure 1.

IOP changes in monkey eyes during 6-hr periods of ketamine anesthesia on consecutive experimentation days. IOP was measured hourly in 3 monkeys for 6 hrs on each of 3 consecutive days per protocol 1. No fluid supplementation was administered at any time. The different symbols represent average IOPs of both eyes of the 3 different animals respectively. The lines represent the mean slopes derived from the average IOPs of all individual monkeys using general linear regression models with repeated measurements. The mean slope $\neq 0.0$ on each day and the difference in slopes between two days $\neq 0.0$ were tested using t-test and contrast based on the fitted models respectively.

Figure 2.

IOP changes in monkey eyes during 6-hr periods of ketamine anesthesia on consecutive experimentation days. IOP was measured hourly in 3 monkeys for 6 hrs on each of 5 consecutive days per protocol 2. No fluid supplementation was administered on days 1 to 4, but a constant intravenous fluid infusion was administered on day 5. The different symbols represent average IOPs of both eyes of the 3 different animals respectively. The lines represent the mean slopes derived from the average IOPs of all individual monkeys using general linear regression models with repeated measurements. The mean slope $\neq 0.0$ on each day and the difference in slopes between two days $\neq 0.0$ were tested using t-test and contrast based on the fitted models respectively.

Figure 3.

IOP changes in monkey eyes during 6-hr periods of ketamine anesthesia on consecutive experimentation days. IOP was measured hourly in 3 monkeys for 6 hrs on each of 5 consecutive days per protocol 3. Fluid supplementation was administered subcutaneously at the end of the 6-hr IOP measurement on days 1 to 4, and a constant intravenous fluid infusion was administered on day 5. The different symbols represent average IOPs of both eyes of the 3 different animals respectively. The lines represent the mean slopes derived from the average IOPs of all individual monkeys using general linear regression models with repeated measurements. The mean slope $\neq 0.0$ on each day and the difference in slopes between two days $\neq 0.0$ were tested using t-test and contrast based on the fitted models respectively.

Figure 4.

IOP changes in monkey eyes during 6-hr periods of ketamine anesthesia on alternating experimentation days. IOP was measured hourly in 6 monkeys for 6 hrs on alternating days 1, 3 and 5 per protocol 4. Fluid supplementation was administered subcutaneously at the end of the 6-hr IOP measurement on each day. The different symbols represent average IOPs of both eyes of the 6 different animals respectively. The lines represent the mean slopes derived from the average IOPs of all individual monkeys using general linear regression models with repeated measurements. The mean slope $\neq 0.0$ on each day and the difference in slopes between two days $\neq 0.0$ were tested using t-test and contrast based on the fitted models respectively.

Table 1

Ketamine Dosing in Different Protocols

Protocols (P)	Mg/kg/day					Mg/monkey/day [*]
	Day 1	Day 2	Day 3	Day 4	Day 5	
P1 (n=3)	91.1±13.4 ^{//}	104.9±12.7 [†]	100.4±7.9 [†]	--	--	382.2±28.9 [†]
P2 (n=3)	76.3±3.6	76.2±2.7	76.1±5.6 [‡]	90.7±5.1	127.0±10.6 ^{//}	252.5±3.2
P3 (n=3)	78.0±1.9 [†]	99.4±7.1	108.1±9.9	109.9±5.5	242.2±14.4 [§]	337.1±75.2
P4 (n=6)	103.1±4.4 [†]	--	110.1±4.5	--	103.6±4.2	343.3±14.8 [†]

Intramuscular ketamine doses (mg/kg/day on indicated days or mg/monkey/day in average) used during IOP measurements from ~8:30 AM to 3:00 PM in different protocols.

Between protocols on each column:

Between days in each protocol:

* Ketamine dosages used on Day 5 in P2 and P3 are not included in the calculation of the average ketamine doses per monkey per day. Data are mean±s.e.m. for n animals. Differences in the ketamine dose between protocols on each column and between days in each protocol were tested by analysis of variance with repeated measurements.

[†] represents P<0.05 for P1 vs. P2, P4 vs. P2, and P3 vs. P4

[‡] represents P<0.01 for P2 vs. P3 or P4

[§] represents P<0.0001 for P3 vs. P2 or P4.

^{//} represents P<0.05 for day 1 vs. day 2 in P1 or day 3 vs. day 4 in P2

^{//} represents P<0.0001 for day 1 vs. days 2-4 in P3 or day 5 vs. days 1-4 in P2 and P3. No significant differences in the ketamine dose between days in P4 were observed.