

**TITLE:** RENAL FUNCTION FOLLOWING CYCLOSPORINE AND ENFLURANE  
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Cyclosporine A (Cys) is a widely used immunosuppressive drug and is currently the most successful agent in prolonging homograft transplant survival. Its use is limited by serious side effects, one of which is nephrotoxicity. Whilst frequently mild, nephrotoxicity, particularly if exacerbated by other nephrotoxic drugs, can limit the dose of Cys tolerated by patients and reduce its effectiveness as an immunosuppressant. Interaction between many different drugs and Cys has been demonstrated, leading to unexpected nephrotoxicity. Inorganic fluoride (F), released during metabolism of fluorinated volatile anesthetics, is potentially nephrotoxic. Because of the potential for multiple procedures requiring anesthesia, patients with transplants can be exposed repeatedly to F. This study was therefore designed to determine the effects of enflurane anesthesia upon renal function in male F344 rats treated chronically with Cys.

To assess renal function prior to Cys, blood samples were drawn and 24-hr collections of urine made for measurement of urea nitrogen (UN), creatinine (Cr) and F. Rats were then gavaged once daily (a.m.) with 0 (Gp 1), 10 (Gp 2) or 20 (Gp 3) mg/kg Cys in corn oil; after 10 days of Cys treatment, renal function was measured again. On the 11th day of Cys treatment, rats were anesthetized for 3 hr with 2.2% enflurane (i.e., 1 MAC). Blood was collected immediately after (0 hr), and at 4, 8, and 20 hr and 2 and 4 days post anesthesia for determination of Cr, UN

and F. Daily 24-hr urine collections were made; volume, Cr, UN and F were measured throughout the study. Cys concentrations were determined by RIA before and after anesthesia.

Cys treatment significantly increased plasma UN values to  $112 \pm 17\%$  of pretreatment values for Gp 2 and  $217 \pm 98\%$  for Gp 3 by Day 10 of treatment (24 hr prior to anesthesia). Cr values at Day 10 were  $74 \pm 12\%$  of pretreatment levels in Gp 1,  $93 \pm 17\%$  in Gp 2, and  $146 \pm 52\%$  in Gp 3. Anesthesia with enflurane resulted in mild, but insignificant, increases in plasma UN or Cr in all groups; urinary outputs were unchanged.

Cys treatment alone decreased F excretion such that the day prior to anesthesia, F excretions in Gp 3 were approximately 40% less than Gp 1. Following enflurane anesthesia, plasma F concentrations (as indicators of enflurane metabolism) were not significantly different among groups (mean peak values 13.2, 10.2 and 10.3 uM, respectively). In contrast, following enflurane anesthesia, F excretions were significantly depressed in Gps 2 and 3 compared to Gp 1; 24-hr F excretions increased approximately 10-fold in Gp 1, 7-fold in Gp 2, but only 5-fold in Gp 3.

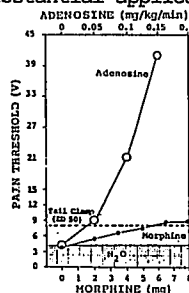
In this study, prior to anesthesia there was a dose dependent Cys-induced reduction of renal F excretion. Post anesthesia, plasma F rose in all groups to a similar level; renal excretion of F was depressed in a dose dependent fashion. Whether decreased F excretion reflects a decreased total amount of enflurane metabolized, a decrease in the ability of the kidney to excrete F, or enhanced uptake of F by bone, is not clear. Although Cys treatment significantly elevated plasma UN and Cr, the addition of a moderate enflurane exposure did not worsen renal function as measured by plasma UN and Cr. (Supported by NIGMS 22746)

## A362

**TITLE:** ANALGESIC ACTIVITY OF INTRAVENOUS ADENOSINE: A COMPARISON OF POTENCY WITH MORPHINE SULFATE  
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**INTRODUCTION:** Adenosine (Ado), an ultra short-acting nucleoside has been shown to reduce anesthetic drug requirements (1,2). Ado may have intrinsic analgesic activity. We planned to evaluate this property, quantitate a dose-requirement, and compare this dosage mg for mg with IV Morphine Sulfate (MS) to establish a potency ratio.  
**METHODS:** We evaluated 6 intubated rabbits (4-5 Kg); spontaneously breathing 60% N<sub>2</sub>O in O<sub>2</sub>. Two forms of noxious stimuli were evaluated: 1) Clamping the tail and the ear with a rubbershod hemostat, 2) Electrical impulses in increasing voltage, as tolerated, to a maximum of 40v; This allows quantifiable, reproducible stimulation. Responses assessed were: HR, SBP, respiratory rate (RR) neurobehavior, and purposeful escape movements. After 20 min of 60% N<sub>2</sub>O, control responses to stimulation were recorded. Ado was infused peripherally, at increasing dosage until significant alterations in response to stimulation occurred. Normotension was maintained without pressure support. Duration and intensity of analgesia was evaluated every 15 min after termination of infusion. Aminophylline was given to reverse analgesic effects. MS was then titrated IV to max 2 mg/kg to attain surgical analgesia (ED 50). No further doses were given if severe respiratory depression occurred.

**RESULTS:** Despite inhalation of 60% N<sub>2</sub>O, all animals responded with purposeful escape movements to tail and ear clamp, and electrical stimulation. Addition of Ado in doses of  $188 \pm 20 \mu\text{g/kg/min}$  completely suppressed the responses to both kinds of stimulation (ED 90). No motor or cardio-respiratory depression occurred, and no ceiling effect was noted. IV Aminophylline (5-10 mg/kg) consistently reversed analgesia. With MS up to 2 mg/kg, no animal had complete suppression of all responses. Fig. and Table summarize the responses.  
**CONCLUSION:** This study demonstrates that IV Ado, in sub-hypotensive doses, significantly raised thresholds for pain. Prolonged analgesia may be mediated by Ado A<sub>1</sub> receptor mechanism as demonstrated by reversal of analgesia with Aminophylline. Ado appears to have an analgesic potency ratio of about 25:1 with IV MS. Adenosine's property of sustained intense analgesia, absent cardio-respiratory depression, absence of "ceiling" effect, and easy reversibility may have substantial application in clinical anesthesia.



**References:**  
 1) Anesthesiology 71(3A):A260, 1989  
 2) Anesthesiology 71(3A):A264, 1989

Table 1. CARDIO-RESPIRATORY DATA

|                          | CONTROL | ADENOSINE | AMINOPHYLLINE |
|--------------------------|---------|-----------|---------------|
| BP (mmHg)                | 97±12   | 101±19    | 105±14        |
| HR (bpm)                 | 240±30  | 230±24    | 242±72        |
| RR (bpm)                 | 89±10   | 85±19     | 47±16*        |
| Pao <sub>2</sub> (mmHg)  | 136±15  | 126±9     | 123±14        |
| Paco <sub>2</sub> (mmHg) | 22±4    | 25±4      | 31±3*         |

n=6, Mean±SD, BP: Systolic BP, RR: Respiratory Rate, \* p<0.05 vs Control