Preliminary observations concerning the effect of dopamine on uranyl nitrate induced renal failure[1]

J.J. Hammond, M.L. Overturf and W.M. Kirkendall

Hypertension Division, Department of Internal Medicine, The University of Texas Medical School at Houston, Houston (Texas 77030, USA) 26 February 1979

Summary. Dopamine infusion, when commenced 24 h after the insult, was ineffective in modifying the course of uranyl nitrate induced renal failure in rabbits.

In 1970 Talley et al.[2] reported that the combination of dopamine and diuretics improved the course of 5 patients with acute renal failure. Lindner et al.[3] administered dopamine and furosemide to dogs with uranyl nitrate induced renal failure. They found that this treatment favorably influenced urine volume, creatinine clearance and distribution of renal blood flow. Using rats, Iaina et al.[4] studied renal failure induced by renal artery clamping. They reported that dopamine, administered simultaneously with the insult, was able to improve renal function.

To examine the proposal that dopamine may be useful in the treatment of acute renal failure, when administered at 24 h after the initial insult, the model of uranyl nitrate induced renal failure was studied[5]. Mature (3.0 kg) male New Zealand white rabbits were used.

High Dose Model (figure 1). Uranyl nitrate 10 mg/kg was given to 7 rabbits. This model was characterized by anuria, progressive elevation of serum creatinine levels, and death. 24 h following uranyl nitrate (10 mg/kg) injection, 4 animals were treated by dopamine infusion. Dopamine in a concentration of 800 µg/ml in 5% dextrose was administered by constant infusion pump for 172 h at a mean rate of 1.1 ml/h. The dose of dopamine administered was 5 µg/kg/min.

The course of the treated rabbits was not significantly different ($p > 0.5$) from that of the control animals, with

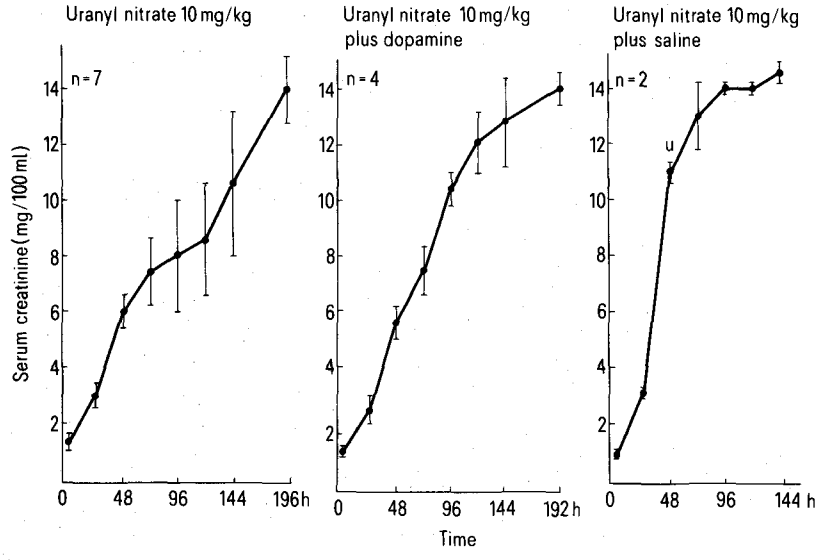

Fig. 1

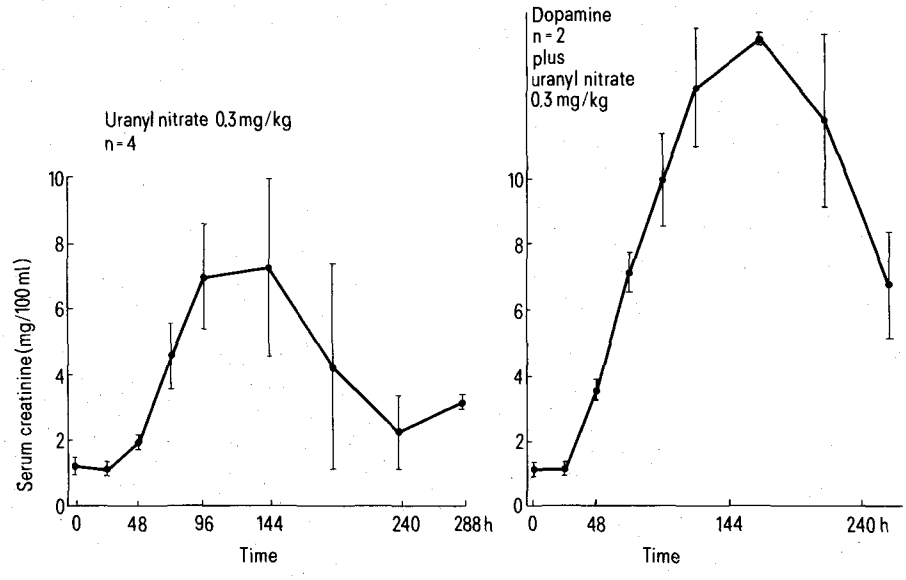

Fig. 2

the occurrence of a progressive rise in serum creatinine, anuria and death. 2 animals were treated with an equivalent volume of normal saline (1.1 ml/h). No significant differences between either the control group, or the dopamine treated group were determined.

Low Dose Model (figure 2). Uranyl nitrate 0.3 mg/kg was given to 4 rabbits. The serum creatinine level rose to a maximum at 144 h, associated with severe oliguria. Following this, the serum creatinine level fell, urine flow returned and the animals recovered. 2 rabbits given uranyl nitrate in low dose (0.3 mg/kg) were treated with dopamine 5 µg/kg/min commencing 24 h after injection. Serum creatinine levels peaked at 168 h. Progressive recovery then occurred in a similar manner to the control group. Dopamine infusion was maintained for 216 h. Although the peak level of serum creatinine shown in the dopamine group is higher than that seen in the control group, this difference is not statistically significant at the 0.05 level.

Discussion. These preliminary results indicate that neither dopamine nor normal saline infusion improved the course of established renal failure induced by uranyl nitrate 10 mg/kg. Similarly, dopamine infusion did not improve the course of established renal failure induced by uranyl nitrate 0.3 mg/kg in this model.

In the canine model of uranyl nitrate induced renal failure, it has been shown that early alterations in the pattern of renal blood flow are seen[6]. However, at 48 h Stein et al.[7], and at 48–96 h, Eisner et al.[8], observed no changes in renal blood flow. Sudo et al.[9] have performed studies of renal hemodynamics during the recovery phase, as well as the initial phase, in uranyl acetate-induced oliguric renal failure in rabbits. They demonstrated that 1 day after injection of uranyl acetate (2 mg/kg) creatinine clearance had dropped to 20% of the control value. Total renal blood flow was reduced, but no alteration in intracortical flow distribution was seen. 3 days after injection, when urine output reached its minimum, total renal blood flow was not significantly different from the control value. They concluded that total renal blood flow per se was not the determining factor responsible for oliguria at that stage.

The use of dopamine in the treatment of acute renal failure is based upon the assumption that a hemodynamic abnormality exists, and that reversal of this abnormality will benefit the course of the acute renal failure. While there is evidence that alteration in renal hemodynamics plays a role in the generation of acute renal failure following a number of insults, including uranyl nitrate, the available data suggest that by 48 h, renal hemodynamics may have returned to normal in the uranyl nitrate model. Thus one may predict that hemodynamic treatments such as those described, would have no benefit when commenced after the generation phase of acute renal failure in this model. Our results obtained are in keeping with this prediction.

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Thioridazine and EKG anomalies[1]

B. Hine, L.J. Traficante, G. Sakalis and S. Gershon

Department of Psychiatry, New York University School of Medicine, New York (New York 10016, USA), 12 March 1979

Summary. Acute i.v. infusion but not daily oral administration of thioridazine-HCl in the dog produced EKG anomalies similar to those reported in psychiatric patients taking this drug. Lack of EKG effects after thioridazine-5-sulfoxide infusion and presence of anomalies after thioridazine at equivalent doses suggests further evaluation of the relationship between reported plasma levels of thioridazine and its ring-sulfoxide in association with EKG changes.

Thioridazine (TZ), a phenothiazine neuroleptic, has been shown to produce anomalies of the electrocardiogram (EKG) consisting of flattening or notching of the T-wave[2-6] in hospitalized psychiatric patients. These effects have been observed at subtherapeutic TZ doses as low as 200 mg/day[2-4] and as soon as 24 h after beginning medication[2].

In the present report, use of an animal model to study these anomalies was attempted by assessing chronic oral administration or infusion of thioridazine hydrochloride in dogs. Thioridazine-5-sulfoxide (TZSO) was also administered in an attempt to determine whether anomalies could be induced by this agent, since the presence of EKG anomalies during TZ administration in schizophrenic patients has been related to elevated plasma levels of this metabolite[6].

Mongrel male dogs, 16–22 kg, received daily oral doses of TZ HCl (6 mg/kg). The EKG was monitored using a modified Einthoven lead II electrode configuration on a Grass polygraph before, and 1.5 and 5.0 h after each daily dose, at least twice weekly for 4 weeks. Despite marked sedation, as well as scleral/conjunctival redness, and the observation of elevated TZSO plasma levels relative to TZ levels (table), no anomalies of the EKG were observed in any of the animals over a 4-week period.

Assessment of EKG effects of direct administration of TZSO, and a comparison with effects of TZ itself, was performed via i.v. infusion in 3 additional dogs, to minimize hepatic biotransformation of each of the agents. Infusion of TZ produced depression of T-wave amplitude to 40–50% of control values. The figure shows this effect in 1 dog after infusion of a cumulative dose of 67 mg (3.4 mg/kg). Sedation was evident before EKG effects were noted, and almost complete EKG (but not behavioral) recovery occurred after an infusion of 84 mg TZ. By contrast, infusion of TZSO (purity verified by TLC) produced no apparent behavioral effects and no change in the EKG after infusion of 64 mg, which represented a cumulative dose of 4.0 mg/kg.

The data indicate that, although the dog may be resistant to EKG-modifying effects of oral TZ when given at doses that on a mg/kg basis approximate those that can produce T-