TITLE: EFFECT OF ORDER OF ADMINISTRATION OF AMRINONE AND DOBUTAMINE ON GUINEA-PIG HEART MUSCLE

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Amrinone has been recommended as an inotropic agent to be used alone or in combination with dobutamine for the failing heart. The purpose of this study was to evaluate the importance of the order of administration of these drugs in achieving the best inotropic effect.

After approval of the protocol by our Animal Review Committee, guinea-pig left atrium was prepared as described by Kobata, et al.[1]. Cumulative dose-response curves were completed for amrinone and dobutamine to determine ED_{50}. Dependent variables (peak twitch, max dp/dt, and max -dp/dt) were measured before addition of drug and at peak effect. Statistics were analyzed with Student's t-test for grouped and paired data, and significance was defined as $p<0.05$.

ED_{50} for dobutamine was 1.5×10^{-7} m/L, and ED_{50} for amrine was 5×10^{-5} m/L. Ten preparations received dobutamine, then amrinone; nine preparations received amrinone, then dobutamine. Percent change from baseline just prior to each drug admininstration was calculated. Results for max dp/dt and max -dp/dt are in the Table; results for percent change in peak twitch tension are shown in the Figure.

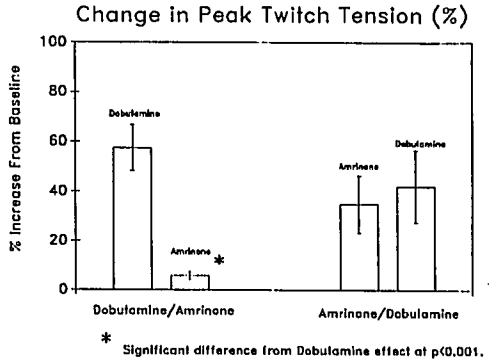
Results show that when dobutamine is administered first, the additional inotropic effect of adding amrinone is small, but significant. When amrinone is administered first, the additional inotropic effect of dobutamine is comparable and significant. These results question the ffectiveness of adding amrinone to an inotropic regimen which already includes dobutamine.

TABLE: PERCENT CHANGE IN	Dobutamine/ Amrinone	Amrinone/ Dobutamine
Max DP/DT	62.8±9.5/ 7.1±1.6†	37.2±11.9/ 48.4±14.8†
Max -DP/DT	75.9±11.6/ 7.6±1.8†	41.7±17.0/ 50.7±16.4†

*Sig diff between groups, $p<0.05$
†Sig diff from dobutamine, $p<0.001$

References

1 J Clin Monit, 5:26-33, 1988.



TITLE: DO EXOGENOUS PORPHYRINS AFFECT ANESTHETIC MANAGEMENT?

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Certain anesthetics, particularly barbiturates, can cause life threatening exacerbations of the porphyrias(1). Porphyrins are now used in humans and laboratory animals for photodynamic (PDT) and neutron capture therapy(NCT) (2,3). These cancer therapies involve porphyrin binding to tumor cells and the subsequent destruction of tumor by light activation (PDT) or neutron beam(NCT). PDT is used intraoperatively in conjunction with surgical resection of high grade gliomas(2); the potential interaction between these compounds and anesthetic agents has not been studied.

Sleep time (time necessary for return of righting reflex) was determined using pentobarbital in male mice with and without prior administration of porphyrin. Group 1 (Control): Pentobarbital 40 mg/kg IV. Group 2: bononated protoporphyrin IX 35 mg/kg IV over 5 min immediately followed by pentobarbital 40 mg/kg IV. Group 3: boronated protoporphyrin IX 100 mg/kg IV over 5 min immediately followed by pentobarbital 40 mg/kg IV. ANOVA was used to detect significant differences between groups.

Group	n	mean sleep time (min.) ±SD	% with loss of toe pinch withdrawal
1	21	50.9±10.7	75%
2	8	33.6±12.1*	0%
3	8	72.9±13.3*+	63%

* $p < .01$ From Control
\+ $p < .01$ From Group 2

There were no mortalities. Mean sleep time was shorter when pentobarbital was preceded by porphyrin 35 mg/kg compared to controls or group 3. Conversely, the higher dose of porhyrin was associated with longer sleep time and caused the animals to appear ill and lethargic. The fact that no animals in group 2 lost toe pinch withdrawal suggests a lighter level of anesthesia in that group. At the lower dose, porphyrins may compete with barbiturate at one of its sites of action. In higher dose, porphyrins may be causing a "porphyria-like" syndrome, increasing the sensitivity to pentobarbital. If these data are applicable to humans, the use of porphyrins may require alterations in anesthetic management. We are currently conducting further studies in this area.

REFERENCES: 1) South Med J 68:29-32, 1975
2) Photochem and Photobiol 46:929-935, 1987.
3) Cancer Research 50:1-9, 1990.