

**TITLE: EFFECTS OF COMBINED TREATMENT WITH NOREPINEPHRINE AND DOPEXAMINE IN HUMAN SEPTIC SHOCK.****AUTHORS:** F. SLOMKA, MD, S. NOUIRA, MD, J.F. VAXELAIRE, MD, F. BRUNET, MD, J.F. DHAINAUT, MD, PhD**AFFILIATION:** Medical ICU, Cochin Hospital, 75674 Paris and Dept. Anesthesiology, Bécélère Hospital, 92140 Clamart, France.

Septic shock is a clinical syndrome characterized by hypovolemia, arterial vasodilation, myocardial depression, and mal-distribution of cardiac output. After correction of plasma volume deficit, if mean arterial pressure (MAP) remains low, the combination of norepinephrine (NE), a  $\beta_1$  agonist, and doxepamine (DPX),  $\beta_2$  and DA1 agonist<sup>1</sup>, may be of interest to improve both tissue perfusion and cardiac performance.

This was an open assessment investigating the effects of DPX in 10 patients (age: 25 to 82 yrs, SAPS: 12 to 32) with septic shock defined as MAP < 60 mmHg and urinary output (UO) < 20 ml/hr despite adequate volume expansion. They received first a NE infusion to maintain MAP > 75 mmHg, followed by a dose titration of DPX from 0.5 to 4  $\mu\text{g}/\text{kg}/\text{min}$ , except for DPX-induced MAP < 60 mmHg. DPX was maintained at the maximal tolerable dose during 36 hrs. MAP, heart rate (HR), pulmonary artery pressure, pulmonary wedge pressure (PWP), cardiac index (CI), systemic vascular resistance (SVR), oxygen delivery (DO<sub>2</sub>) and consumption (VO<sub>2</sub>), UO, and arterial lactate were evaluated at control (NE alone) and at each level of DPX and during long term infusion up to 36hrs. Statistical analysis was performed using 2 way ANOVA. The protocol was approved by our ethical committee.

All patients received 2 $\mu\text{g}/\text{kg}/\text{min}$  without any hemodynamic changes. 4 patients did not tolerate full dose of

DPX (2 of them died < 36hrs) Only 6 patients then received 4 $\mu\text{g}/\text{kg}/\text{min}$  of DPX, and their results are summarized in the Table. PWP declined from 16.8 to 11.3 (p<.01). Arterial lactate levels rose from 3.65 to 5.60 mmol/l, associated with a small increase in DO<sub>2</sub> (17%) and VO<sub>2</sub> (9%). During the long term infusion of DPX, SVR progressively declined (-39%, p<.05), lactate levels fell below the baseline values (-31%, p<.01), and CI and DO<sub>2</sub> increased (42 and 17%, respectively, NS), with no change in VO<sub>2</sub>. UO rapidly increased (115% after 6 hrs, NS) and remained elevated.

The surprising biphasic changes of arterial lactate observed during the NE and DPX infusion may be due to: (1) a transient worsening of tissue perfusion by NE or (2) a "wash-out" effect of the vasodilating properties of DPX. It is difficult to solve this pathophysiological problem in the absence of significant change in DO<sub>2</sub> and VO<sub>2</sub>, in the small group of patients (6/10) who tolerated 4 $\mu\text{g}/\text{kg}/\text{min}$  of DPX.

The combination of NE and DPX may improve tissue perfusion and UO in some patients with septic shock. The beneficial effect of this treatment needs a multicenter study to confirm these preliminary results.

Reference: 1) Cardiovascular Drug Reviews. 7:141-159, 1989.

	CI l/min/m <sup>2</sup>	HR	SVR IU	DO <sub>2</sub> ml/min/m <sup>2</sup>	VO <sub>2</sub> ml/min/m <sup>2</sup>	lactate mmol/l
DPX						
control	3.91	113	14.7	513	157	3.65
2 $\mu\text{g}/\text{kg}/\text{min}$	4.46	129	12.0	580	159	4.54
4 $\mu\text{g}/\text{kg}/\text{min}$	4.43	127	13.0	603	171	5.60*

**A142****Title: Isradipine for Treatment of Hypertension during Abdominal Surgery****Authors:** B Dartayet, A Edouard, K Samii**Affiliation:** Dept Anesthésie, Université Paris-Sud, Hôpital de Bicêtre, France

Isradipine (ISR) is a new dihydropyridine calcium blocker with potent vasodilating effects<sup>1</sup>. Efficacy and safety of an iv dose of ISR were prospectively tested vs placebo in the treatment of intraoperative hypertension (HT) during abdominal surgery.

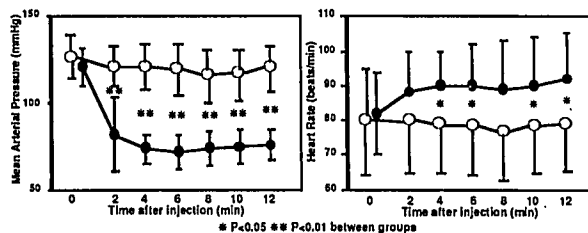
**Methods.** After approval by the IRB, the study was conducted on patients (pts) under general iv anesthesia. All pts who were potential candidates for intra-operative HT gave their informed consent during preoperative visits. Pts entered the study if their mean arterial pressure (MAP, Dinamap®) remained >110 mmHg 5min after an additional injection of fentanyl (4 $\mu\text{g}/\text{kg}$ ). They randomly received in a double blind manner 0.5mg of ISR or placebo in 10ml over 5min. Immediately before (T<sub>0</sub>) up to 12min (T<sub>12</sub>) after the start of infusion, MAP was measured every 2min. At T<sub>12</sub> pts were called (1) 'Responders' if MAP was <110mmHg and  $\Delta\text{MAP} \geq 10\text{mmHg}$  vs T<sub>0</sub> (target parameter), further measurements at 5min intervals were taken up to T<sub>45</sub>, (2) 'Non Responders' if MAP was >110mmHg and/or  $\Delta\text{MAP} < 10\text{mmHg}$  vs T<sub>0</sub> and received on an open basis 0.5mg ISR in 10ml over 5min at T<sub>15</sub>. After the start of the 2nd infusion, MAP was measured every 2min up to 12min (T<sub>27</sub>), then every 5min for the remaining period (T<sub>30</sub>-T<sub>60</sub>). **Efficacy parameters** were Responder Rate at T<sub>12</sub> and Time from beginning of 1st infusion until target parameter was reached. **Safety parameters** were the number of pts who developed hypotension (MAP < 70mmHg) and/or tachycardia ( $\Delta\text{Heart Rate (HR)} > 20\text{bpm}$  vs T<sub>0</sub>). Fisher exact test and t-test adjusted by Bonferroni procedure were used as appropriate. Data are expressed as mean  $\pm$  SD.

**Results.** Table shows that 23 pts were included in the study. No difference was noted between groups before inclusion. Responder

rate was higher in ISR group (P<0.0001). Target parameter was reached within 2 min (figure: ISR ● Placebo ○). Finally ISR was given in 21 patients (blind 12; open 9). MAP remained between preoperative and postinduction levels during the 45min period following ISR. Hypotension was noted in 3 pts (14%) 6 to 8 min after start of ISR. Significant increase in HR between groups was only noted during blind period and 1 pts exhibited a  $\Delta\text{HR} > 20$  bpm.

**Comments.** As previously described for nifedipine<sup>2</sup>, iv bolus of ISR is an easy and effective mean to treat intra-operative HT. However the magnitude and the promptness of MAP reduction as well as the side effect profile observed in the study suggest that 0.5mg administered over 5min may be a relative high dose and/or infusion rate for some pts.

	ISR (n = 12)	Placebo (n = 11)
Age (yrs)	56 $\pm$ 12	60 $\pm$ 13
Weight (kg)	63 $\pm$ 13	63 $\pm$ 10
History of HT (n)	5	5
Preoperative MAP(mmHg)	99 $\pm$ 6	100 $\pm$ 12
Postinduction MAP(mmHg)	79 $\pm$ 11	80 $\pm$ 14
Preinclusion MAP(mmHg)	121 $\pm$ 11	126 $\pm$ 12
Responder Rate (%)	100	9

**References**

1. Van den Berg EK, Dehmer GJ. Am J Cardiol 61: 1102-5, 1988
2. Begon C, Dartayet B, Edouard A et al. J Cardioth Anesth 3: 707-11, 1989