TITLE: EFFECTS OF COMBINED TREATMENT WITH NOREPINEPHRINE AND DOPAMINE IN HUMAN SEPTIC SHOCK

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Septic shock is a clinical syndrome characterized by hypovolemia, arterial vasodilatation, 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 and β1 agonist, and dopexamine (DPX), β2 and DA1 agonist, 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 μg/kg/min, except for DPX-induced MAP < 60 mmHg. DPX was maintained at the maximal tolerable dose during 36 hrs. MAP, heart rate (HR), systolic arterial pressure, pulmonary wedge pressure (PWP), cardiac index (CI), systemic vascular resistance (SVR), oxygen delivery (DO2) and consumption (VO2), 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 institutional committee.

All patients received 2μg/kg/min without any hemodynamic changes. 4 patients did not tolerate full dose of DPX (2 of them died < 36hrs) Only 6 patients then received 4μg/kg/min of DPX, and their results are summarized in the Table. PWP declined from 16.8 to 11.3 (p<0.01). Arterial lactate levels rose from 3.65 to 5.60 mmol/L, associated with a small increase in DO2 (17%) and VO2 (9%). During the long term infusion of DPX, SVR progressively declined (~39%, p<0.08), lactate levels fell below the baseline values (~31%, p<0.01), and CI and DO2 increased (42 and 17%, respectively, NS), with no change in VO2. 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 DO2 and VO2, in the small group of patients (6/10) who tolerated 4μg/kg/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.


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Title: Isradipine for Treatment of Hypertension during Abdominal Surgery

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Isradipine (ISR) is a new dihydropyridine calcium blocker with potent vasodilating effects. 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 (4μg/kg). They randomly received in a double blind manner 0.5mg of ISR or placebo in 10ml over 5min. Immediately before (T0) up to 12min (T12) after the start of infusion, MAP was measured every 2min. At T12 pts were called (1) 'Responders' if MAP was <110mmHg and ΔMAP ≥10mmHg vs T0 (target parameter), further measurements at 5min intervals were taken up to T45. (2) 'Non Responders' if MAP was ≥110mmHg and/or ΔMAP<10mmHg vs T0 and received on an open basis 0.5mg ISR in 10ml over 5min at T15. After the start of the 2nd infusion, MAP was measured every 2min up to 12min (T27), then every 5min for the remaining period (T30-T60). Efficacy parameters were Responder Rate at T12 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 (ΔHeart Rate (HR) >20bpm vs T0). Fisher exact test and t-test adjusted by Bonferroni procedure were used as appropriate. Data are expressed as mean±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 blank period and 1 pts exhibited a ΔHR > 20 bpm.

Comments. As previously described for nitrordipine*, 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.

References: