Pharmacologic treatment of acute respiratory failure

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DIFFERENT SURFACTANT TREATMENT STRATEGIES FOR RESPIRATORY FAILURE INDUCED BY HYDROCHLORIC ACID ASPIRATION IN RATS

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Introduction Aspiration of gastric contents is one of the most feared complications of general anesthesia and is known to be an important cause of the adult respiratory distress syndrome (ARDS). Hydrochloric acid (HCL) damages the alveolar-capillary membrane leading to intra-alveolar hemorrhage and accumulation of plasma proteins. It is known that these proteins inhibit normal surfactant function in a dose-dependent way A study was designed to investigate the effect of different treatment strategies with an exogenous surfactant preparation on lung function of rats suffering from respiratory failure after intratracheal HCL instillation.

Methods The studies were performed in 34 male adult Sprague-Dawley rats (body weight: 300-350 g). The animals were anesthetized, tracheotomized, paralyzed and ventilated by a Siemens Servo ventilator 900C at the following ventilator settings: pressure-controlled ventilation, FiO2=1.0, ventilation frequency=30/min, peak airway pressure (Ppeak)=14 cm H2O, PEEP=2 cm H2O and I/E ratio=1:2. After reaching steady state (PaO2 > 500 mmHg) all rats received HCL intratracheally (0.1 N; 3 ml/kg). PEEP was increased to 6 cm H2O and Ppeak to 26 cm H2O. After PaO2 decreased < 200 mmHg, the animals were divided into 5 groups: Group I (n=7) was only ventilated; Group II (n=8) received surfactant intratracheally; Group III (n=7) was lavaged with saline followed by intratracheal surfactant instillation; Group IV and V (n=6 in both groups) were lavaged with saline or a diluted surfactant suspension, respectively. The amount of saline used for all bronchoalveolar lavages was 30 ml/kg at 37 C; the amount of surfactant in the diluted surfactant suspensions was 100 mg/kg. The surfactant concentration for intratracheal instillation (Groups II and V) was at a dose of 200 mg/kg. Blood samples for measurement of PaO2 were taken from the carotid artery of each animal before intratracheal HCL instillation, every 15 min post-instillation and 5, 30 and 60 min after treatment.

Results Just before treatment (after HCL instillation) there were no significant differences in PaO2 values between all groups (mean ± SD: 139.4 ± 39.7 mmHg). Five minutes after treatment there was a significant increase in PaO2 values in Groups III and IV (288.1 ± 111.1 and 338.2 ± 61.6 mmHg, respectively). There was a further decrease in PaO2 values in Groups I and IV (103.6 ± 25.8 and 86.3 ± 41.9 mmHg, respectively). The PaO2 values in Group II did not increase significantly (168.6 ± 46.2 mmHg).

Conclusion These results demonstrate that gas exchange can be improved by lavaging the lungs with saline, followed by surfactant instillation, or by lavaging lungs with a diluted surfactant suspension. An explanation is that by means of lavage, plasma proteins, which are known to be potent surfactant inhibitors [1,2], are removed from the alveoli. These results should be considered for treatment with surfactant of patients suffering from respiratory failure after HCL aspiration.

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REDUCED INCIDENCE OF NOSOCOMIAL PNEUMONIA (NP) AND SHORTER ICU STAY IN INTUBATED PATIENTS (PTS) WITH THE USE OF SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT (SDD). A multicentric, double-blind, placebo-controlled study. M. SANCHEZ, J.A. CAMBRONERO, J. LOPEZ, E. CERDA, J.M. RODRIGUEZ, J. RUBIO, S. ROGERO, A. NUNEZ. Hospitals: Príncipe de Asturias, Alcalá de Henares; La Paz, Cruz Roja and Doce de Octubre, Madrid; Severo Ochoa, Leganés. SPAIN.

In most of the published studies SDD prevents NP in ventilated PTS. Not all of them are controlled studies, and in only a few SDD reduces associated morbidity and mortality. Five general ICUs participated in this controlled trial on the effectiveness of SDD in preventing NP and reducing its associated morbidity and mortality in intubated PTS. SDD (gentamicin, polymyxin E and amphotericin B) or placebo (PL) was applied q6h to the oropharynx and through the nasogastric tube. In uninfected PTS iv Ceftriaxone or iv PL was additionally infused for the first 3 days, 2 g., once per day. The PTS were followed until death or discharge from ICU. We randomized 270 Pts, 226 were analysed. SDD/PL PTS were similar in age (55/54), sex, and diagnosis, and severely ill on admission (mean APACHE II score 26/26). SDD of gram negative bacilli (GNB) was achieved in 3 to 10 days and was associated with a significant reduction of incidence (22%/48%, p<0.001) and number of episodes of NP (29/79, p<0.001). In survivors duration of intubation (11/20 days, p=0.007), mechanical ventilation (11/16 days, p=0.02), and ICU stay (17/24 days, p=0.04) was shorter. Non-respiratory tract infections were also less frequent (18%/35%, p=0.03). Global mortality was similar in both groups (38%/47%).

Our SDD regimen significantly reduces colonization by GNB, as well as the incidence of NP and other infections, length of intubation, and ICU stay in a general population of ventilated ICU Pts. We could not find a significant reduction in mortality.

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POSOLOGICAL INDIVIDUALIZATION OF AMINOPHYLLINE IN AN INTENSIVE CARE UNIT

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The aim of this study was to determine a standard dose of aminophylline to be administered to patients interned in Intensive Care Units due to severe respiratory failure.

Material and Methods - 16 patients (90♂) with an average age of 62.8 (± 12,9 years) on mechanical ventilation due to severe respiratory failure (13 COPD, 2 status asmaticus and 1 Pickwick syndrome) were given aminophylline in continuous perfusion in a dose varying between 0.43 and 0.51 mg/kg/h according to body weight. The theophylline plasma concentration was measured by a fluorescent polarization immunoassay (TDx system, Abbott Diagnostics) at 2 and 12 hours after the onset of administration and daily thereafter at 9 am. The pharmacokinetic study was divided into two phases. In the first (at 12 hours), total body clearance was determined using the Chiou method. The second phase corresponded to the equilibrium state and the following formula was used: $Cl = \frac{D}{Css}$.

Results - A statistically significant difference was found between the total body clearances in Phase 1 and Phase 2 (Δ= 0.014 ± 0.012 L/h/kg $p < 0.05$) this confirming the significant intraindividual variability ($p<0.05$) of the total body clearance capacity of the patients. 12 patients (75%) presented total body clearance values close to 0.028 ± 0.005 L/h/kg.

Discussion - The inter and intraindividual variation in body clearance could be foreseen in this sample. It was possible to establish, through the simulation of administration, that 0.5 mg/h/kg of the ideal body weight (IBW) was the most convenient dose for these patients. When 0.4 mg/h/kg IBW was given, subtherapeutic levels were reached in 7 patients and 0.6 mg/h/kg IBW attained toxic values in 3 patients.

Conclusions - 0.5 mg/h/kg IBW of aminophylline permitts a safe and satisfatory therapy. Periodic controls should be carried ou every 3 days to allow for eventual posological readjustments.

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ROLE OF ALMITRINE-INDUCED PULMONARY ARTERIAL PRESSURE (PAP) INCREASE ON GAS EXCHANGE IMPROVEMENT.

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One of the hypothesis concerning PaO2 increase secondary to Almitrine (Alm) infusion in ARDS patients is pulmonary vessels recruitment induced by PAP increase. To analyse this hypothesis, we studied 7 patients mechanically ventilated in the post operative period after coronary bypass graft surgery. Inclusion criteria: normal right ventricular function; cardiac index (CI) > 2.5 l/min/m2; no pulmonary, renal and hepatic failure; no cardio or vasoactive drugs. We measured mixed venous and arterial blood gases, pulmonary and systemic hemodynamic parameters after: I/ I hr of hemodynamic, ventilatory and temperature stability = TO; 2/ I5 min of G-Suit (GS) inflation (35 mmHg on the legs, 20 mmHg on the abdomen) = TI; 3/ I5 min of Alm infusion (2-4 mcg/kg/min), GS still inflated = T2; 4/ a recovery period of 90 min = T3; 5/ novel I5 min Alm infusion (same dose) while GS was deflated in order to maintain a similar PAP than T3 = T4.

RESULTS:

AP(mmHg)	PaO2(mmHg)	PvO2(mmHg)	PAP(mmHg)	CI(l/min/m2)	
82 ± II	I08 ± 33	33 ± 5	I4 ± 4	3.3 ± .7	TO
88 ± I4	I09 ± 3I	33 ± 6	I7 ± 4°	3.4 ± .7	TI
90 ± I4	I28 ± 32°§	35 ± 5	2I ± 5°§	3.6 ± .9	T2
88 ± I2	III ± 32	34 ± 6	I6 ± 4	3.4 ± .7	T3
85 ± I5	I25 ± 33°§	35 ± 4	I7 ± 4°	3.4 ± .8	T4

° : $p < .0I$ vs TO; § : $p < .0I$ vs TI

AP = mean arterial pressure; PvO2= O2 venous pressure.

DISCUSSION: GS inflation increased PAP without change in PaO2. Alm significantly improved PaO2 to the same extent whether PAP was increased (T2 vs TI) or not (T4 vs TI). This suggests that gas exchange improvement secondary to Alm infusion is not necessarily dependent on PAP increase.

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EFFECTS OF INTRAVENOUS N-ACETYLCYSTEINE(NAC)ON RESPIRATORY FUNCTION IN ACUTE LUNG INJURY(ALI)

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To determine whether i.v.NAC has beneficial effects in patients with mild-to-moderate ALI in terms of ventilatory support(VS),FIO2 requirements,evolution of the lung injury score(LIS),development of severe lung injury(ARDS)and mortality rate,we prospectively enrolled 61 adult patients with ALI to receive either NAC 40 mg/kg/day or Placebo(PL)during 3 days.Respiratory dysfunction was assessed daily considering the need of VS,the FIO2 necessary to achieve a PaO2 of 70 to 80 mmHg and the evolution of 3 components of the LIS (chest X-ray,PaO2-FIO2 ratio and respiratory system compliance).Data were collected at baseline (day 0),on the first 3 days after admission to the ICU and on discharge.NAC and PL groups(32 vs 29 patients)were comparable at entry in terms of SAPS and values of the LIS.At day 0, 69% of the patients were ventilated in the NAC group versus 76% in the PL group;at day 3, 83% of the NAC treated patients did not require any further VS, versus 52% in the PL group(p=0.01).PaO2/FIO2 improved significantly(p=0.05)from day 0 to day 3 only in the NAC group.The LIS showed a signifi - cant improvement(p=0.003)in the NAC treated group within the first 10 days of treatment;no change was observed in the PL group.3 patients in each group progressed to ARDS.The one-month mortality rate was 22% for the NAC and 35% for the PL group **In conclusion**,early treatment with NAC seems to affect favourably pulmonary gas exchange and decrease the need for prolonged VS in patients with mild-to-moderate ALI.

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EFFECTS OF APROTININ IN HEMORRHAGIC COMPLICATIONS OF PATIENTS WITH ARDS TREATED BY ECCO2R-LFPPV.

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Bleeding remains a troublesome complication in pts with ARDS under ECCO2R-LFPPV, and seems related to the persistant activation of coagulation-fibrinolysis system as a consequence of blood contact with foreign surfaces, despite the use of heparin. Aprotinin, a broad-based proteinase inhibitor, has been successfully used to decrease bleeding in open heart surgery (Ann Thorac Surg 1987; 44: 640), but has never been evaluated in pts with bleeding during prolonged by-pass. The aim of this study was to assess the effects of aprotinin infusion (2.10^6 KIU intra-venously, and 5.10^5 KIU/h in constant infusion) in 11 ARDS pts who experienced bleeding and enrolled in a prospective clinical trial of a cohort of 40 pts treated by ECCO2R-LFPPV. This subgroup developed 14 episodes of acute hemorrhage. 9 episodes were spontaneous: bleeding appeared at the insertion sites of the catheters and bronchial suctions became hemorrhagic with biological signs of hyperfibrinolysis (group I), and 5 episodes were due to hemothorax related to a pleural drainage during by-pass (group II). In group I, bleeding rapidly vanished in 8/9 cases after aprotinin infusion with progressive improvement of coagulation abnormalities (Table 1), while no effect was observed in group II ($p<.008$, Fisher's test). No difference was observed in SAPS, OSF, Murray's score, and presence of sepsis between the 2 groups.

TABLE 1

		Fb (g/l)	PT (%)	APTT (sec)	D-dimers (µg/ml)	RBC (u/day)
Group I	H0	3.2	60	70	9.5	3.7
	H24	3.1	58	116	5.1*	1.7
Group II	H0	2.6	48	105	3.9	9.4
	H24	1.8	42	121	6.0	17**

Fb = fibrinogen, PT = prothrombin time, APTT = activated partial thromboplastin time, RBC = red blood cells, * p≤.05 H0 vs H24, ** Group I vs II.

These preliminary results suggest that bleeding occurring during ECCO2R-LFPPV is able to vanish after aprotinin infusion, except in cases of hemothorax related to pleural drainage. Thoracotomy at the bedside only may cure such a bleeding.

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Respiratory mechanics II

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AUTOMATIC COMPENSATION OF TUBE RESISTANCE IN CPAP AND IPS

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Background: In CPAP with inspiratory pressure support (IPS) the level of support is independent of the patient's inspiratory effort. However, the resistive work of breathing increases progressively with inspiratory flow due to the flow-dependent resistance of the endotracheal tube (ETT). **Question:** How can we modify the airway pressure generated by the ventilator in order to compensate the resistive work caused by the ETT independently of the ventilatory pattern? **Investigations:** In the laboratory we measure the pressure drop across commercial endotracheal tubes (ΔP_{ETT}) at sinusoidal flow, V'max = ± 2 l/s; f = 15/min. Results separated for inspiration and expiration are fitted to the equation [1]

[1] $\Delta P_{ETT}(t) = K_1 \cdot V'^{K2}$.

At the patient we measure flow (V') and airway pressure (P_{aw}) and calculate intratracheal pressure (P_{trach}) in real time using the formula [2].

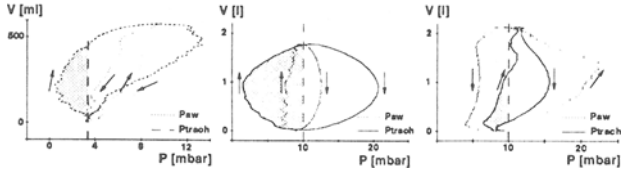
[2] $P_{trach}(t) = P_{aw}(t) - \Delta P_{ETT}(t)$

To compensate ETT resistance, inspiratory pressure support must be increased by the current pressure drop across the ETT. To this end we access the demand flow control of a ventilator by feeding back an error signal P_{aw}-P_{SP} generated by an external unit, where P_{SP} is the set point of the airway pressure calculated as follows:

[3a] $P_{SP}(t) = PEEP + \Delta P_{ETT}(t) + IPS$ (inspiration)

[3b] $P_{SP}(t) = PEEP + \Delta P_{ETT}(t)$ (expiration)

with V(t) = actual volume, IPS = inspiratory pressure support. **Results:** The coefficients for an ETT of 8 mm ID and 323 mm length were found to be K_1=8.21, K_2=1.94 for inspiration and K_1=9.18, K_2=1.75 for expiration. Using these coefficients, the continuously measured airway pressure/volume curve and the calculated intratracheal pressure/volume curve can be superimposed. Fig. 1 shows a breath with PEEP = 3.4 mbar and IPS = 5 mbar. Despite inspiratory pressure support, considerable additional ventilatory work occurs. In Fig. 2 we measured p_{aw} and p_{trach} with CPAP = 10 mbar at sinusoidal flow (V'_{max} = 1.3 l/s) generated by a lung simulator (C = 50 ml/mbar). Fig. 3 shows the same breath but with a ventilator modified according to equ. 3. Additional work due to the ETT is notably reduced. **Consequences:** In spontaneous breathing with inspiratory pressure support the dominant resistive work is caused by the ETT and is markedly influenced by gas flow, i. e. by the patient's ventilatory pattern. A continuously adapted pressure support permits a minimum of additional ventilatory work with a minimum of pressure load.



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WORK OF BREATHING AND PRESSURE TIME PRODUCT DURING BIPHASIC POSITIVE AIRWAY PRESSURE AND ASSISTED SPONTANEOUS BREATHING VENTILATION.

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The aim of our study was to compare the respiratory efforts in terms of work of breathing of patient (WOBpat, [J/l]), work of breathing of ventilator (WOBvent, [J/l] and pressure-time-product (PTP, [cmH_2O*s/min]) during assisted spontaneous breathing (ASB, a ventilator technique synonym to pressure support ventilation) and biphasic positive airway pressure (BiPAP).
We studied 19 intubated patients during weaning after cardiac surgery. The patients were breathing spontaneously and supported by equivalent pressure levels with both respirator modes (BiPAP Phigh 15 and 10cmH_2O, Plow 5cmH_2O, Thigh 2s, Tlow 4s, abbreviated B15 and B10; ASB pressure support 15 and 10cmH_2O, CPAP 5cmH_2O, abbreviated A15 and A10). The WOB was calculated by the Campbell's diagram method, the PTP was obtained by integration of the area between the chest wall static recoil pressure and the esophageal pressure curve.

Results (mean±SD):

	WOBtot	WOBvent	WOBpat	PTP
B15	1.19±0.07	0.94±0.10+	0.26±0.13+	92±42+,*
A15	1.21±0.10	0.97±0.10+	0.23±0.13+	57±24+,*
B10	1.18±0.18	0.61±0.09+	0.57±0.22+	136±44+,*
A10	1.20±0.18	0.70±0.10+	0.50±0.18+	104±28+,*

+ means p<.01 B15 vs. B10 and A15 vs. A10
* means p<.01 B15 vs.A15 and B10 vs. A10

We conclude that both modes are suitable for reducing spontaneous respiratory efforts by increasing ventilator support, but BiPAP is more exhaustive as shown by higher PTP levels.

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