PHARMACOKINETICS OF MIDAZOLAM IN INFUSION FOR LONG-TERM SEDATION OF VENTILATED PATIENTS IN ICU.

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Sedation is necessary to improve patient comfort, attenuate the stress response and facilitate mechanical ventilation. Midazolam a water soluble benzodiazepine with a faster onset of action and a shorter elimination half-life than other drugs, has become popular and is now increasing its usage in the ICU setting. The aim of our paper is the quantitation of plasma concentration of Midazolam needed to obtain adequate sedation. Six patients who were due for ventilation for at least 24h., age 66 ± 9 , weight 73 ± 13 , Apache II index 23 ± 5 , received one initial dose of Midazolam 0.3mg/kg followed 15 min after by continuous infusion. During the first 24h to facilitate mechanical ventilation, a initial bolus dose of the neuromuscular blocking drug Vecuronium 0.1mg/kg were administered followed by continuous infusion (abolition of the 3rd or 4th response to ulnar nerve train of four supramaximal stimulation) during at least 24h. Determinations of Midazolam were carried out by extraction of 5ml of blood, centrifuged, plasma separated and stored deep-frozen until analysis. Blood samples were taken at the following intervals: pre dose -2-5-15-30 min -1-2-4-8-12-24-36-48-60h. A sensitive and selective HPLC assay using UV detection at 254 nm for quantitation was used. (Hewlett-Packard 1050 Autosampler, U-Bondapak columns C18, 10 μm .). Pharmacokinetics parameters were calculated from each patient according to standard formulae. The data were fitted to a bi-compartmental model using an own program based on iterative methods.

Midazolam Infusion range was 30-164h (mean 63h). During the initial bolus phase: $V_d \text{ cent. compart.} = 233\text{ml/kg}$. $T_{1/2\alpha} = 6.5 \text{ min}$ and Mean Residence Time (Tres med) = 90min. During the infusion phase: Clearance = 94ml/kg/h . $V_d \text{ steady state} = 109\text{ml/kg}$. The mean plasma concentration for therapeutic window was $430 \pm 126 \text{ ng/ml}$. At the end of infusion, recovery was obtained without antagonize in $53 \pm 26 \text{ min}$.

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Cardiovascular assessment II

THORACIC ELECTRICAL BIOIMPEDANCE (TEB) VS THERMODILUTION (TD) FOR CARDIAC OUTPUT (CO) MEASUREMENT DURING MECHANICAL VENTILATION

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TEB is a non-invasive technique for haemodynamic monitoring. Some reports concern situations influencing the measurements performed with TEB, particularly in critically ill patients (pts) (sepsis, haematocrit variations and mechanical ventilation). In this study we compared CO measurements obtained with TEB and with TD in pts under mechanical ventilation. CO was measured before induction of general anaesthesia and about 10 minutes after orotracheal intubation and connection to ventilator. 17 pts (age $46-72$, BSA $1.6-1.97 \text{ m}^2$, haematocrit 30%-40%) were included in our study. All the pts underwent the same kind of ventilation: 12 breaths/min with tidal volume $8-10 \text{ ml/kg}$. CO measurements with TD were performed injecting 10 ml of saline solution at room temperature. The recorded value is the average of three measurements. TEB data were recorded using a BoMed MCOM3 device, considering the average of one minute recording. In non-ventilated pts the mean TD-CO was $5.96 \pm 1.29 \text{ (SD) l/min}$ and the mean TEB-CO 5.77 ± 1.52 . The equation is $Y = 1.059 X - 0.537$ with $r = 0.896$ ($p < 0.0001$). In the same pts under mechanical ventilation the mean TD-CO value was $5.67 \pm 1.44 \text{ l/min}$, while the mean TEB-CO was 5.89 ± 1.88 . The equation is $Y = 0.896 X + 0.813$, with $r = 0.688$ ($p < 0.002$). For a more accurate evaluation of the data we plotted the difference between the two measurements (TD-CO - TEB-CO) by mean CO (TD-CO + TEB-CO / 2) as suggested by Bland and Altman (Lancet, 1986). We obtained the following information: the mean difference between the techniques in non-ventilated pts was 0.18 ± 0.16 , while in ventilated pts was -0.22 ± 0.33 . The CO values measured using these two methods are similar; the differences are quite slight and there are no major variation for different flow levels. In ventilated pts the difference, though increasing, remains acceptable for clinical purposes. Only in one case the results of the two techniques disagreed. Therefore it can be stated that, due to its easy use, non-invasivity, continuous data reading, and relatively low cost, TEB can be considered a useful technique for haemodynamic monitoring of critical pts.

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PROPOFOL versus MIDAZOLAM IN SEDATION OF CRITICALLY ILL PATIENTS. COST-BENEFIT ANALYSIS

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Propofol (2,6-di-isopropylphenol) is an intravenous anaesthetic agent which has been favourably compared with midazolam in continuous sedation of patients undergoing mechanical ventilation. Its use reduces the time needed for recovery of spontaneous respiration. One of the disadvantages which can limit its general use in critical medicine is its high cost. So far, no clinical study has been able to demonstrate whether a possible reduction in length ICU stay in patients sedated with propofol would be of benefit in reducing the economical cost of such stays.

The purpose of this study is to evaluate and compare the safety, clinical effects and economical cost of propofol and midazolam in the sedation of ICU patients undergoing mechanical ventilation.

One hundred-fifty critically ill patients were studied and randomly allocated to receive short-term (less than 24 hours), medium-term (24 hours-7 days) and prolonged (more than 7 days) continuous sedation with propofol (n=78) or midazolam (n=72). Both groups were comparable with respect to age, sex, weight, diagnosis at admission, severity of illness (valued following the Simplified Acute Physiologic Score) and basal conscience levels (determined by the Glasgow Coma Score modified by Cook). Mean duration of sedation with propofol (11.8 hours, 117.1 hours and 313.5 hours for the subgroups of short, medium and prolonged-term sedation, respectively) was similar to that of subgroups treated with midazolam (11.7 hours, 113.1 hours and 342.3 hours, respectively). Mean doses required were 2.36 mg/kg/hr of propofol and 0.17 mg/kg/hr of midazolam. Patients in the propofol group showed a percentage of sedation hours at the desired level of 93%, compared with 82% ($p < 0.05$) in the midazolam group. No differences between groups were observed with respect to hemodynamics, O₂ transport and analytical parameters. Both agents were considered safe with respect to the induction of adverse reactions during their use in prolonged sedation.

Recovery after interrupting sedation was significantly faster in patients treated with propofol (1.0 $\pm$ 0.2, 2.8 $\pm$ 1.0, 5.2 $\pm$ 2.1 hours for extubation, and 2.1 $\pm$ 0.5, 5.5 $\pm$ 1.9, 9.9 $\pm$ 3.6 hours for total recuperation, for short-term, medium-term and prolonged-term sedation subgroups, respectively) than in those sedated with midazolam (3.6 $\pm$ 0.8, 20.6 $\pm$ 5.6, 46.6 $\pm$ 12.2 hours for extubation, and 6.3 $\pm$ 1.5, 26.2 $\pm$ 8.2, 68.4 $\pm$ 13.8 hours for total recovery, for short-term, medium-term and prolonged-term sedation subgroups, respectively). In patients sedated with propofol, total consciousness recovery was predictable according to sedation time ($r = 0.97$, 0.99, 0.92 for short, medium and prolonged-term sedation subgroups, respectively), while this correlation was not observed in the midazolam group. Compared with midazolam, in subgroup of sedation of less than 24 hours, propofol provided a cost-savings of approximately 1,900 pts per patient, due to shorter ICU stays. In the subgroup of more than 24 hours sedation, and compared with midazolam, propofol had the same quantifiable cost, but constituted a greater indirect benefit due to money saved on the cost of antagonisation with flumazenil.

In our hospital environment, propofol is a sedative agent with the same safety, higher clinical effectiveness and better cost-benefit ratio than midazolam in continuous sedation of critically ill patients.

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DETERMINATION OF CARDIAC OUTPUT, OXYGEN CONSUMPTION AND OXYGEN DELIVERY: A SIMULTANEOUS COMPARISON OF THREE DIFFERENT NON-INVASIVE METHODS WITH STANDARD METHODS

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Evaluation of oxygen transport variables cardiac output (C.O.), oxygen consumption (VO₂), and oxygen delivery (DO₂) is a tool to guide therapy and predict outcome for critically ill patients. Standard methods with considerable invasiveness for measurement of these variables are:
- C.O. by thermodilution (CO_{TD}, HP CMS Monitor Hewlett Packard)
- VO₂ by indirect calorimetry (VO₂ CAL, Datex Deltrac Metabolic Monitor)
- arterial (SaO₂M) and mixed venous (SvO₂M) oxygen saturation and hemoglobin concentration (Hb.M) by hemoximetry (OSM 3 Hemoximeter, Radiometer Copenhagen)

Methods:

In this study the reliability of three different non-invasive methods for determination of C.O., VO₂ and DO₂ were examined by simultaneous measurement of VO₂ by indirect calorimetry, measurement of mixed expired carbon dioxide concentration (F_{ECO2}) by a capnometer (Datex-Noracorp) and measurement of minute ventilation (VE) by a flow calibrated ventilator (Evita, Dräger). Oxygen saturations were measured by pulse oximetry (SaO₂PDX, HP CMS Monitor) and by hemoximetry from a central venous blood sample (SvO₂M). C.O. was also measured by thoracic bioimpedance (AVL 2001 Monitor, BoMed, CO_{BI}).

In 15 postoperative mechanically ventilated patients with hemodynamic monitoring including radial artery and pulmonary artery catheters all these mentioned variables were simultaneously determined in 88 cases and calculated according to the formula:

Standard:	C.O.	=	CO _{TD}
	VO ₂	=	VO ₂ CAL
	DO ₂	=	CO _{TD} * SvO ₂ M * 13.9 * Hb.M / 100
Fick-method:	CO _{FICK}	=	VO ₂ CAL / (SaO ₂ PDX - SvO ₂ M) * 13.9 * Hb.M / 100
	VO ₂	=	VO ₂ CAL
	DO ₂	=	CO _{FICK} * SaO ₂ PDX * 13.9 * Hb.M / 100
Modified Fick-method:	CO _{FickM}	=	(F _{ECO2} * VE) / (SaO ₂ PDX - SvO ₂ M) * 13.9 * Hb.M / 100
	VO ₂	=	VO ₂ FickM = F _{ECO2} * VE * 0.9 [F _{ECO2} conv. to STPD]
	DO ₂	=	CO _{FickM} * SaO ₂ PDX * 13.9 * Hb.M / 100
Bioimpedance:	C.O.	=	CO _{BI}
	VO ₂	=	VO ₂ FickM
	DO ₂	=	CO _{BI} * SaO ₂ PDX * 13.9 * Hb.M / 100

Results:

Standard vs.	C.O.	VO ₂	DO ₂
Fick-Method	r=0.83	-	r=0.81
Modified Fick-Method	r=0.86	r=0.81	r=0.85
Thoracic bioimpedance	r=0.66	r=0.81	r=0.58

Conclusion:

In our experience we found the non-invasive determination of C.O., VO₂ and DO₂ by the Fick-method using indirect calorimetry, pulse oximetry and a centr. ven. blood sample and by a modified Fick-method using capnometry and spirometry as well as pulse oximetry and a centr. ven. blood sample to be reliable alternatives to thermodilution-derived parameters. Thoracic bioimpedance did not correlate with T.D. as close as the Fick-methods.

201

ROLE OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN INTENSIVE CARE UNIT PATIENTS

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In the last few years Transesophageal Echocardiography (TEE) has become an extremely helpful tool for assessing cardiac function in critically ill patients. Nevertheless, in our opinion, TEE is underutilized in the intensive care setting because of lacking confidence in its potential benefits to solve clinical problems. In order to evaluate the indications of TEE in a multidisciplinary intensive care unit, we reviewed our four years experience extrapolating all critically ill patients not previously submitted to cardiac diagnostic procedures. 78 patients underwent 105 examinations, the age range was 17 - 82 years and the weight range was 42 - 98 kilos. Although the most frequent indication was monitoring left ventricular function and its pharmacological support, other indications were typically diagnostic. These included: unsatisfactory cardiac assessment by traditional monitoring (28 pts.), unexplained hypotension (8 pts.), acute respiratory distress (7 pts.), suspected aortic dissection (6 pts.), systemic embolization (5 pts.), cardiac evaluation of donor patient (5 pts.). All TEE examinations were satisfactory for imaging. TEE was always the conclusive examination when left ventricular function was under investigation, showing pitfalls and limitation of pulmonary artery catheterization. In conclusion TEE may have a great role in solving clinical problems at the bedside often avoiding transport of the critically ill patients to the diagnostic laboratory. Consequently underutilization of this recent technique is a matter of difficult availability of expensive equipment and trained personnel rather than lacking indications in the intensive care unit setting.

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203

THE PROGNOSTIC VALUE OF ATRIAL PACING-HANGRIP AND CORONARY RESERVE AFTER UNCOMPLICATED ACUTE MYOCARDIAL INFARCTION.

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We have studied the prognostic value of atrial pacing (AP) combined with hangrip exercise (APHG). It was performed in 66 consecutive patients 5 to 10 days (mean 6,39 days) after uncomplicated acute myocardial infarction (UAMI).

Basal test was positive (depression of the ST segment) in 33 patients (28 with AP and 5 with APHG). A second test after 1 mgr. of sublingual nitroglycerin shifted negative in 13 patients for a similar or greater double product (present reserve) and continued being positive in 20 patients (absent reserve coronary).

During a follow-up of 12 months, 11 cardiac events had: 2 cardiac deaths, 3 recurrent myocardial infarction, 2 coronary by-pass surgery, 3 unstable angina and 1 heart failure.

Multivariate discriminant analysis identified absent coronary reserve as the best predictor of morbimortality. It was able to classify to 80% of all patients for combined cardiac events and 83% for hard cardiac events. With help of ejection fraction, accuracy was of 93% for hard cardiac events.

Thus, our results showed that atrial pacing combined with handgrip exercise and coronary reserve, evaluated by vasodilator, were a useful means of classifying patients at the time of Coronary Unit discharge after UAMI according to the likelihood of having cardiac events during the ensuing 12 months.

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202

FREQUENCY OF BACTERIEMIA ASSOCIATED WITH TRANSESOPHAGEAL ECHOCARDIOGRAPHY (TEE) IN INTENSIVE CARE UNIT (ICU) PATIENTS (pts). H. Mentec*, S. Terré, and P. Legrand.

In cardiologic pts, the incidence of bacteremia during TEE has been shown to be low enough (1.4 to 3.2 %) to avoid antibioprophylaxis. ICU pts might be at higher risk of bacteremia because of widespread colonization of upper gastrointestinal tract with potentially pathogenic microorganisms and mucosal injuries due to instrumentation. To determine the infectious hazard associated with TEE in ICU pts, we conducted a prospective study in 89 pts (mean age 57). Blood samples were systematically drawn for aerobic and anaerobic culture before (BC1), at the end of (BC2) and 30 mn after (BC3) TEE examinations in ICU pts. The mean duration of TEE was 39 mn (15-120). Eighty six pts were on ventilator, 78 had a nasogastric tube. Thirty pts had underlying conditions that usually justify antibioprophylaxis of bacterial endocarditis before high risk procedures such as gastrointestinal endoscopy. Twenty six pts did not receive any antibiotic at the time of TEE. In 76 pts, the three BC were negative. In one pt, BC1 grew *Enterococcus faecalis*, BC2 and BC3 were sterile. In one pt, the three BC grew *Staphylococcus aureus* and BC1 also yielded *Enterobacter cloacae*. A contamination (only one positive BC out of the three) with coagulase negative staphylococci occurred in 2 BC1, 3 BC2, and 4 BC3. In one pt treated with cefotaxime and netilmicin, BC1 was sterile and BC2 and BC3 yielded coagulase negative staphylococci. In one pt receiving no antibiotic, BC1 was sterile and BC2 and BC3 yielded *Enterococcus faecalis*. None of these last two pts then received a specific antibiotic treatment nor developed any bacterial determination. Thus, the overall frequency of bacteremia induced by TEE was 2.2% (2/89). The frequency did not differ whether the pts received antibiotics before TEE (1/63, 1.6%) or not (1/26, 3.8%) (NS). Therefore, antibioprophylaxis does not appear justified before TEE in ICU pts.

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204

EARLY RECURRENT ISCHEMIA EVALUATED WITH HOLTER.

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The incidence, characteristics and prognostic significance of early ST-changes after acute myocardial infarction (AMI) evaluated with Holter monitoring are not well established.

We have studied prospectively 83 patients with AMI, Killip class I and II, all under 65 years of age (53.6 ± 9.1). The site of the AMI was anterior in 35 and inferior in 48. The maximum mean value of CPK was 1830 ± 230 U/L. 56 patients received thrombolytic therapy (group T). Holter was performed for 48 hours, with 2 leads to detect local and at distance ischemia, on the 2nd and 3rd day of the AMI. The rise or depression of the ST-segment according to the 1x1x1 rule were accepted as criteria of positivity (H+) in the absence of previous tachycardia and/or postural changes. A coronariography was performed in the two first weeks post-AMI. Death, reinfarction, need of aorto-coronary By-pass or PTCA were considered as criteria of adverse outcome.

H+ was observed in the 31.1% (26/83) of cases (15 in the zone of AMI, 6 at distance and 5 in both). A rise in the ST was observed in 15 cases, a depression in 6 and both in 5. Early post-AMI angina occurred in 22.9% (19/83), 13/26 (50%) of H+ and 6/57 (10.5%) of H- (p 0.001). An adverse outcome was observed in 14/26 (53.8%) of H+ and in 6/57 (10.5%) of H- (p 0.01). Multivessel lesions occurred in 15/26 (57.6%) of H+ and in 24/57 (42%) of H- (N.S.).

There were no significant differences in incidence of early angina and H+ between the group T (19.6%, 30.3%) and the group no T (29.6%, 33.3%).

We conclude that Holter detected early ST changes post-AMI is a frequent finding associated with early post-AMI angina and adverse outcome. Multivessel disease and thrombolysis don't appear to affect its incidence.