TITLE: CAN SERUM TNF OPEN A THERAPEUTICALLY RELEVANT DIAGNOSTIC "WINDOW" IN SEPTIC PATIENTS ?

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Mortality of the septic syndrome is around 40-60% and can rise to 100% if multiple organ failure (MOF) develops. It is generally assumed that the high mortality of sepsis can only be reduced by early diagnosis and prevention of subsequent MOF. The aim of our study was to investigate the validity of TNF-alfa determination for the early diagnosis of septicemia and, in combination with the MOF-score (1), to define a "window" during which an anti-TNF-agent could be applied with the greatest chance of success.

METHODS: Serum TNF-alfa was measured and the MOF-score was calculated daily in 87 ICU patients. TNF serum levels were determined by means of an IRMA (Medgenix, Belgium). Sepsis was diagnosed in 24 patients according to clinical criteria. The MOF-score was used to assess the severity of multiple organ failure. Data were analysed using the SAS software package (SAS Institute, Cary, NC) and are expressed as mean+/- SEM.

RESULTS: The mean values of all sequential TNF determinations were significantly higher in the septic patients as compared to the nonseptic patients (73.2+/-4.3 vs. 8.5+/-0.4; p<.01). Similarly, the maximum TNF values were significantly higher in the septic group (156.9+/-26.5 vs. 20.1+/-2.3; p<.01). By setting the cut-off point at >/< 40pg/ml to differentiate between sepsis and nonsepsis we calculated a sensitivity of 70.8%, a specificity of 98% and a diagnostic accuracy of 91.3%. None of the patients with a TNF level above 250pg/ml survived. Mortality was 80% above a TNF concentration of 200pg/ml, whereas only 40% of patients with a TNF-max. below 150pg/ml died.

Max. MOF-scores were significantly higher for septic than for nonseptic patients (10.6+/-0.3 vs. 4.8+/-0.2; p<.01). The septic nonsurvivors exhibited scores that were significantly higher than those of the septic survivors (11.2+/-0.4 vs. 9.8+/-0.4; p<.05).

To differentiate between survival and nonsurvival we set a cut-off point at MOF>/<8 and calculated a sensitivity 89% and a specificity of 82%.

Maximum MOF scores were attained with a latency of 33+/- 13.8 hours after the determination of max. TNF serum levels.

CONCLUSION: Sequential TNF-alfa serum level determinations are useful for the diagnosis and prognosis of septicemia. We found a direct temporal connection between max. TNF serum levels and the development of septic shock. MOF max. followed TNF max. by a mean of 33 hours. This latency may represent the therapeutic "window" during which an anti-TNF-agent, e.g. a monoclonal anti-TNF-antibody, could be applied as a logical therapeutic consequence. In order to identify this window in a clinical setting we suggest that a diagnostic kit to enable quick detection of rising TNF-alfa serum levels should be developed.

1.): Goris RJA, Boekhorst TPA, Nuytinck JKS, Gimbrere JSF: Multiple organ failure: generalized autodestructive inflammation? Arch. Surg. 120:1109-1115; 1985

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TITLE: TOLERANCE AND HYPERLIPEMIA DURING LONG-TERM SEDATION WITH PROPOFOL

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Propofol (Diprivan^{R}), a recently approved intravenous sedative-hypnotic, is becoming increasingly popular for sedation in the I.C.U. Questions remain regarding tolerance development during prolonged infusions and the effect of the lipid-containing emulsion formulation on serum lipid levels.

After obtaining informed consent, we studied 22 ventilator-dependent I.C.U. patients, ages 19-76 yr, receiving propofol sedation by continuous infusion for 12 - 336 hr (mean 78±17 hr) according to an IRB-approved protocol. The propofol infusion rate was adjusted to maintain a stable level of sedation and daily propofol requirements were recorded. Serum levels of cholesterol, free fatty acids and triglycerides were measured before initiating the infusion (pre-inf) and immediately before discontinuing the infusion (end-inf). Data are reported as mean ± SEM.

Propofol was a safe and effective sedative with a consistently rapid recovery. Loading doses ranged from 0.03-0.8 mg/kg (mean 0.3±.05 mg/kg). Maintenance doses ranged from 0.6-13.8 mg/kg/hr and tended to increase with duration of infusion, particularly in those cases where the infusion period exceeded 7-8 days (fig. 1). Lipid levels were not significantly altered by the propofol emulsion at infusion rates below 6 mg/kg/hr, but increased dramatically when infusion rates exceeded this level (fig. 2).

Our experience indicated that propofol is a useful sedative for critically ill patients, particularly when rapid recovery is desired. Our results are in agreement with Gottardis et al.[1] that low-level propofol infusions of 3 days duration are not associated with significant effects on serum lipid levels. However, during more prolonged infusions, tolerance can develop to the sedative effects of propofol with increasing maintenance requirements. With propofol infusion rates exceeding 6 mg/kg/hr, administration of a large lipid load can significantly increase serum lipid levels.

Reference

1. Gottardis M, Khunl-Brady K, et al., Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations. Br J Anaesth 62:393-96, 1989.

Figure 1

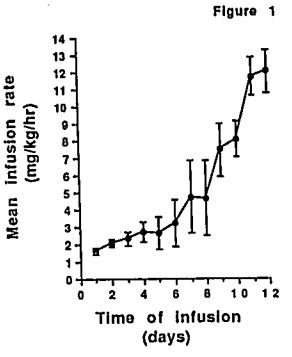

Figure 2