Immunomodulating Effects of Fentanyl and Ketamine in Severe Human Sepsis

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Introduction: Immunomodulating effects of analgesics and sedatives are still insufficiently described[1] and were mostly studied in healthy volunteers, which may not adequately mirror the effects in the critically ill. This study investigated the impact of fentanyl (Fen) and ketamine (Ket) on the pattern of cytokine response in severely septic patients compared to healthy volunteers.

Methods: With IRB approval and informed consent, we prospectively studied 26 ventilated patients with severe sepsis (ACCP/SCCM criteria[2]) and 6 healthy volunteers. Septic patients (Table) were randomly assigned to receive continuous infusions of either Fen (1 Φg/kg/h) or Ket (1 mg/kg/h), both combined with a background infusion of midazolam (0.05 mg/kg/h), started at the described dosages and then titrated to a Ramsay score of 4-5.[3] After 3 days of infusion, blood was collected and processed as described earlier.[4] Cytokines (TNF, IL-10) were assayed by ELISA in whole blood cultures stimulated ex vivo with 1 Φg/ml of LPS (E. coli 0111:B4). Furthermore, blood was withdrawn from healthy volunteers and analyzed as described above: in the absence of drugs (= control) and after addition of Fen ($4.16\ 10^{-7}$ M) or Ket ($5.89\ 10^{-4}$ M; data from our laboratory.[4]) Statistics: ANOVA with $p<0.05$ as statistically significant; data are mean ∀ SE.

Results: LPS-stimulated TNF release remained unchanged after addition of Fen, but was significantly decreased with Ket in whole blood obtained from healthy volunteers (Fig.) . In severely septic patients, LPS-stimulated TNF release was significantly (6-12 times) lower than in healthy individuals. Furthermore, LPS-stimulated TNF release was significantly lower in septic patients after 3 days of Ket instead of Fen infusion (Fig.). Parallely, LPS-stimulated IL-10 release (pg/ml) remained unaffected, both in healthy volunteers (control 47.8∀19.4, Fen 70.7∀28.0, Ket 44.8∀9.7) and in septic patients (Fen 80.2∀15.3, Ket 42.2∀16.2).

Conclusions: Compared to healthy volunteers, LPS-stimulated TNF response was significantly diminished in severely septic patients indicating a profound monocyte hyporesponsiveness. Irrespective of the individual clinical condition (healthy or severely septic) and in contrast to Fen, the administration of Ket suppresses the proinflammatory (TNF) cytokine release, whereas the antiinflammatory response (IL-10) is obviously unaffected. Whether these Ket effects should be judged "protective" as suggested[5] or detrimental remains to be elucidated.

Septic patients	Fentanyl (n=13)	Ketamine (n=13)	p
Age (yrs)	59.9∀4.4	59.3∀3.8	n.s.
APACHE II score	27.3∀1.6	31.2∀1.4	n.s.
MOF score	9.7∀0.4	10.3∀0.6	n.s.
Leukocytes (10^3/Φl)	21.8∀2.2	17.5∀2.5	n.s.
Lactate (mmol/l)	2.9∀1.1	2.5∀0.6	n.s.