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Clinical factors that modify the therapeutic efficacy of Midazolam during sedation of critically ill paediatric patients.

Midazolam (MDZ) is one of the most commonly used sedatives within paediatric intensive care units (ICU); however, when administering therapeutic doses (200 µg/kg/h) of the generic drug, the desired effect is not observed, requiring doses of up to 1200 µg/kg/h, implying a greater possibility of adverse effects. The aim of this study is to analyse the clinical factors that modify the therapeutic efficacy of MDZ in critically ill paediatric patients who require deep sedation. Thirteen patients aged 1-18 years were included. They received an initial dose of 200 µg/kg/h in continuous infusion. Three mL blood samples were drawn at 1, 3, 12, and 24 h post-dose, 3 h after the first dose decrease, and 3 and 24 h after concluding the treatment. Plasma MDZ (P-MDZ) levels were quantified by an HPLC method and pharmacokinetic parameters were determined with Winnonlin 2.1 software. At the same time, sedation was monitored by means of the Bispectral Index (BIS) considering that a score <60 corresponds to deep sedation. Demographic (sex, age, weight) and biochemical (total bilirubin [TB], alanine aminotransferase [ALT], glucose [BG] and albumin [ALB]) data were registered.

Parameters	**Median**	**Interval**	**Normal Values**
BG (mg/ dL)	119,91	75-214	60-100
ALT (UI/L)	178,1	22-228	5-30
TB (mg/dL)	2,1	0,05-9,04	0,3-1,0
ALB (g/dL)	2,3	1,45-3,5	3,8-5,4
Cl (L/kg/h)	0,027	0,001-0,092	0,192-0,798
T ½ (h)	49,52	13,86-138,6	2,9-4,5
MDZ dose (µg/kg/h)	508,3	100-1200	100-300
P-MDZ 24h after the first dose (ng/mL)	4607,5	713,58 - 10 000	100-1000
BIS	59,2	32-80	< 60

Regarding BG, higher levels might be due either to infection or to the MDZ continuous infusion during ICU stay, the latter has been previously described (1) as a result of many conditions, including metabolic response to injury. ALT and TB increases may reflect hepatocellular damage and a consequent reduction of CYP3A activity (2), which would also explain a low MDZ Cl and a long t½. At 24 h post-dose, we found the highest P-MDZ, with low ALB. Since MDZ is 96-98% bound to albumin, lower ALB would condition an increase in free MDZ concentrations (3).

Median values for P-MDZ and MDZ dose were 4607,5 ng/mL and 508,3 µg/kg/h respectively, with BIS scores of 59,2, indicating that doses higher than the established were needed to obtain deep sedation. There are no available studies reporting MDZ therapeutic range or expected concentrations to obtain deep sedation in paediatric patients in ICU; only in adult patients sedation has been reported to correspond to P-MDZ levels of 100-1000 ng/mL (4).

In spite of a small study population, these results show a tendency to therapeutic failure with generic MDZ, since higher doses are needed to achieve sedation. It is also advisable to monitor the hepatic function panel, including TB, ALT, ALB, and BG, as well as BIS, in critically ill patients who require deep sedation using MDZ to avoid adverse effects.

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