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Drug-Specific PK-Informed Residual Sedative Burden Model Better Explains Time to Anesthesia Release Than Cumulative Dose

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Background

Cumulative dose ignores when drugs were given and how much remains at case end.[1] Published pharmacokinetic (PK) models can estimate this residual exposure for each drug: propofol, dexmedetomidine, and midazolam.[2–4]

Objective

Test whether modeled end-of-case sedative levels explain release time better than cumulative dose, and compare release times by dominant sedative.

Methods

Design. Retrospective study of 383,508 general anesthetics. Outcome: time from anesthesia stop to anesthesia release (end of anesthesia provider care).

Exposure. PK models estimated central-compartment concentrations at anesthesia stop, scaled to drug-specific references (residual burden, B):

$$B_{drug} = C_{drug}(\text{anesthesia stop}) \div C_{reference,drug}$$
$$B_{total} = B_{propofol} + B_{dexmedetomidine} + B_{midazolam}$$

Models. Log-linear regression compared cumulative doses, summed burden, and drug-specific burdens, adjusting for age, preoperative weight, case duration, volatile use, and intraoperative opioids (morphine milligram equivalents).

Profiles. Cases with B_{total} ≥ 1.0 were grouped by the drug contributing >60% of burden, or "mixed."

Interpretation

- Keeping drugs separate preserved information that is lost when they are combined into one score.
- Shorter release with higher propofol burden may reflect technique, case type, or workflow rather than faster recovery from propofol.

Modeling each sedative's residual burden separately explained release time modestly better than cumulative dose; combining them into one score did worse.

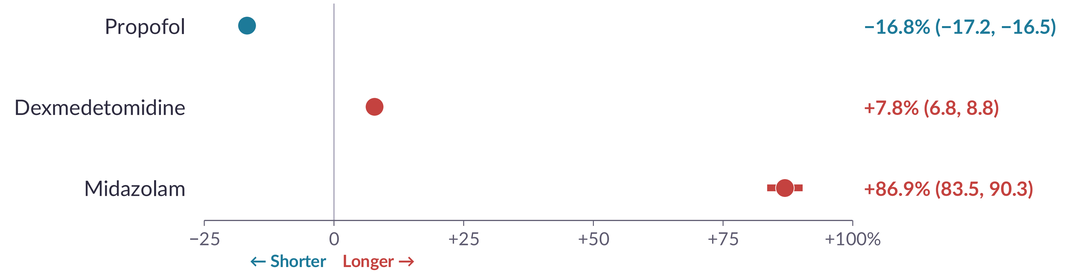
383,508 general anesthetics with median release time of **82.3 min** (IQR 40.9–130.8)

A. Model fit by exposure measure

Exposure measure	R^2	AIC
Cumulative dose, per drug	0.3923	928,755
Summed residual burden	0.3846	933,610
Residual burden, per drug (best fit)	**0.3991**	**924,499**

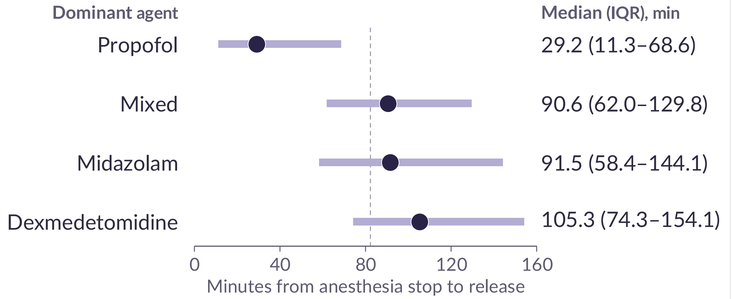
ΔR^2 **+0.0068** vs cumulative dose; lower AIC = better fit.

B. Adjusted association with anesthesia release time



Adjusted % difference per 1-unit normalized burden (95% CI); all three drugs in one model.

C. Unadjusted release time by residual profile



Cases with B_{total} ≥ 1.0, grouped by dominant drug. Median (IQR); dashed line = full-cohort median (82.3 min). Kruskal–Wallis P < 0.001.

Limitations

- Retrospective design; unmeasured procedural differences, patient factors, anesthetic technique, or care setting may contribute to associations.
- Drug levels were estimated from PK models, not measured, and do not directly capture sedative effect.
- Anesthesia release marks the end of anesthesia provider care, a workflow endpoint rather than a direct measure of awakening.
- Profile comparisons were unadjusted and depend on burden scaling.

Conclusion

In this cohort, separate drug-specific residual burdens modestly improved fit versus cumulative doses; a summed burden did not. These associations do not establish that changing sedative dosing would shorten recovery.

Next steps

1. Add opioid kinetics and richer case-mix data.
2. Test incremental value beyond clinical, cumulative-dose, and simple dose-timing models.
3. Evaluate calibration and generalizability before clinical use.[5]

References

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