

Authors

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Title:

A Phase IIa, Randomized, Controlled, Double-Blind, Dose-Finding Study Evaluating the Safety and Pharmacodynamics of CNS 7056 in Patients Undergoing Diagnostic Upper GI Endoscopy

Abstract:

A new benzodiazepine anesthetic/sedative, CNS 7056, has been developed to permit a predictable fast-onset, short duration of action and fast recovery. This has been achieved by rendering the compound susceptible to hydrolysis by non-specific tissue esterases to an inactive metabolite. We report the first patient study.

A Phase II, midazolam controlled study was conducted in 9 sites throughout the US. 100 patients requiring a diagnostic upper GI endoscopy were randomized to 1 of 4 treatment groups (25 each) - a single dose of CNS 7056 (0.10, 0.15, or 0.20 mg/kg), or midazolam (0.075 mg/kg). Subjects received no pre-medication other than a benzocaine throat spray for scope insertion as required, and were on room air throughout the procedure. Sedation was assessed using the MOAA/S scale, and readiness for discharge by the Aldrete score. Success of the procedure was assessed using a composite endpoint (MOAA/S \leq 4 for 3 consecutive measurements, completion of procedure, no requirement for rescue sedative, & no manual or mechanical ventilation). Safety was assessed using standard safety assessments, with particular attention to pulse oximetry and airways management.

The onset of and recovery from sedation with CNS 7056 was rapid, with the time to fully alert appearing to be faster than, and more consistent than midazolam (Table 1). The overall procedure success rate varied from 32-64% in the CNS 7056 groups in a dose related manner, compared with 44% for midazolam (Table 1).

As this was a single dose study, any additional sedative medication was regarded as rescue. In the midazolam group, 44.0% of patients did not require rescue medication, versus 32.0%, 56.0% and 64.0% in the CNS 7056 dose groups (0.10, 0.15 and 0.20 mg/kg respectively). Time to ready for discharge was short in all treatment groups (ITT: 14.0, 12.8 and 11.8 mins at 0.10, 0.15 & 0.20 mg/kg CNS 7056 respectively, 17.2 mins with midazolam). Times were shorter in all treatment groups when patients with rescue medication were excluded.

Despite the patients being on room air there was no dose dependent drop in O₂ sats, there were no requirements for ventilation, and the incidence of hypoxia was low (~20%), mainly mild in nature, of short duration, and similar across all groups. Vital signs remained stable, no serious adverse events were reported. The rate and nature of adverse events in the CNS 7056 groups was similar to the midazolam group.

Table 1

	Procedure Success (ITT) n/n (%)	Time to Fully Alert (MOAA/S) (mean \pm SD, ITT)
CNS 7056 (0.10 mg/kg)	8/25 (32.0%)	11.0 \pm 10.04

CNS 7056 (0.15 mg/kg)	14/25 (56.0%)	13.4 ± 6.51
CNS 7056 (0.20 mg/kg)	16/25 (64.0%)	12.1 ± 5.26
Midazolam (0.075 mg/kg)	11/25 (44.0%)	17.2 ± 16.71