Extending Survival Time on a Disabled Submarine by Reversible Pharmacological Intervention — A First Look

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Background:

Reversible pharmacological intervention to reduce CO_2 production and O_2 consumption by a disabled submarine (DISSUB) crew was evaluated.

Materials and Methods:

Oral diazepam was used for sedation, which was reversed by intra-nasal Flumazenil. In a single blind, repeated measures design, 6 subjects were given diazepam-placebo for 48 hrs. CO_2 and O_2 exchange was recorded every 2.5 hrs during around-the-clock bed-rest, in a climate-controlled chamber (Fig. 1). Furthermore, the subjects' movements were assessed with a wrist-worn actigraph. Meals and cognitive testing 2x / day were preceded by Flumazenil-placebo administration. Return to the "sedated" state was induced by administering diazepam-placebo. In the 48 hr Drug-phase, the schedule was repeated, diazepam (10–40 mg) was given, followed by maintenance doses to yield a clinical "Alertness Score" of 3 (responds only after name is called loudly or repeatedly) or 4 (lethargic response to name spoken in a normal tone) (see Table 1). Sedation was reversed before meals/testing with Flumazenil administration and finally 30 minutes before study end at hour 96.

Results:

Subjects received a total of 360–495 mg of diazepam (Table 2); individual doses were 5–40 mg per administration; average alertness score was 3.75. Mean VCO_2 was 0.248 L/min under Placebo; mean VCO_2 was 0.212 L/min under Drug, a significant drop of 14% (Table 3). Subjects consumed less O_2 in the Drug-arm (Placebo VO_2 = 0.272 L/min; Drug VO_2 = 0.236 L/min; significant

Fig. 1: Subjects' confined living area: a 2.4 m high x 5.8 m long x 4.0 m wide stainless steel walled room. Temperature was kept at 24ºC, humidity below 50%, with low lighting and minimal noise.

Results (continued):

13% reduction) (Table 4). Subjects were 21-36% less active under diazepam, as assessed by their actigraphs (Fig. 2). The mean Flumazenil dose for awakening from sedation to fully alert state was 0.36 mg. Subjects were conversant and oriented within 5 min after receiving the Flumazenil, performing cognitive tasks at 86–97% of their Placebo baseline. Six hrs after final Flumazenil dosing, subjects could follow instructions and ambulate independently, though unsteadily. After 72 hrs, cognitive and physical functioning returned to normal levels.

Table 1. Scale Used by the Observer to Assess Alertness/Sedation of Subjects

Response	Score Level
Responds readily to name spoken in normal tone	5 (Alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to noxious stimulus	0

Table 2. Diazepam Dosing Summary

	Total Diazepam (mg)	Occasions given over 48 hrs	Dose range	# 5 mg	times given 10 mg	15 mg	20 mg	25 mg	30 mg	40 mg
Grp I										
S11	420	29	5-30	2X	15X	0	10X	0	2X	0
S12	360	24	5-30	3X	8X	1X	11X	0	1X	0
S13	360	30	5-25	11X	8X	0	10X	1X	0	0
Mean	**380**	**27.7**								
Grp II										
S21	415	20	10-40	0	6X	1X	6X	0	6X	1X
S22	495	21	10-40	0	4X	1X	8X	0	8X	1X
S23	495	23	5-40	2X	3X	1X	9X	0	6X	2X
Mean	**468**	**21.3**								

Table 3. Carbon Dioxide Production and Alertness Scores

	Placebo	Diazepam		
Alertness Score:	5.0	[5.0]	4.5 – 4.0	3.5 – 3.0
$VCO_{2(L/min)}$	**.248**	[.261]	**.211***	**.209***
N =	*112*	*[16]*	*58*	*35*

** statistically different from placebo*

Table 4. Oxygen Consumption and Alertness Scores

	Placebo	Diazepam		
Alertness score:	5.0	[5.0]	4.5 – 4.0	3.5 – 3.0
$VO_{2(L/min)}$	**.272**	[.281]	**.236***	**.232***
N =	*112*	*[16]*	*58*	*35*

** statistically significant difference from placebo*

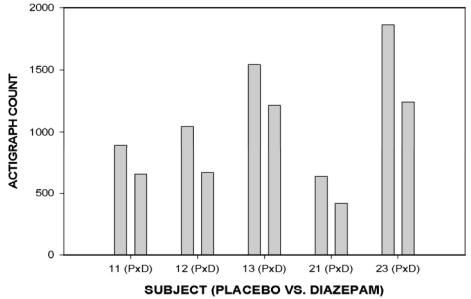

Fig. 2: Total physical activity of 5 subjects under placebo (P) and diazepam (D)

Conclusions:

Reversible sedation to lower subjects' metabolism was effective, safe and practical. It is speculated that, under the severe stress of an actual DISSUB situation, the relative gain from this approach may be even greater.

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