Resistant Alcohol Withdrawal: Does an Unexpectedly Large Sedative Requirement Identify These Patients Early?

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ABSTRACT

Introduction: While most patients with alcohol withdrawal (AW) respond to standard treatment that includes doses of benzodiazepines, nutrition and good supportive care (non resistant alcohol withdrawal-NRAW), a subgroup may resist therapy (resistant alcohol withdrawal-RAW). This study describes a distinct group of AW patients, their sedative requirements, and hospital courses.

Methods: Over a period of 6 months, AW patients requiring 50 mg diazepam IV in the first hour were followed. We recorded admission indices and diazepam doses with vital signs at 1, 2, 3, 6, 12, and 24 hours. Patients were considered to have RAW if they required additional sedatives for control of symptoms and/or were having persistent abnormal vital signs despite the physicians' choices of therapy.

Results: Nineteen patients were enrolled; all had similar admission indices. While the 4 NRAW had normal vital signs within 3 hours, all 15 RAW patients had abnormal vital signs; 15 RAW patients required escalating diazepam doses—14 required barbiturates, 7 were intubated, and 5 had hypotension. Comparing groups: interval and total diazepam doses were not different at 1,2, and 3 hours; interval doses at 6 and 12 hours, and total doses at 6, 12, and 24 hours were significantly different.

Conclusions: RAW patients require large doses of benzodiazepine administration, additional sedatives, and undergo complicated hospitalizations.

INTRODUCTION

Treatment for patients with the alcohol withdrawal (AW) syndrome includes administration of appropriate sedative agents, supportive care with repletion of substrates, and careful evaluation for associated conditions such as pneumonia, hypoglycemia, electrolyte abnormalities, occult trauma, and infection. Although patients with very mild AW are effectively treated with an oral benzodiazepine (BZD), those with more severe withdrawal require the administration of an intravenous BZD such as diazepam [1–3]. Additionally, there may exist a subset of patients not previously described as a group who have resistant alcohol withdrawal (RAW); that is, patients in whom their AW is refractory to typical doses of intravenous BZD. Since these patients often require exceedingly high doses of BZD to control their psychomotor agitation (e.g. profound tremor, confusion, formicating, pulling at restraints) and related vital sign abnormalities (hypertension, tachycardia, increased temperature), many are treated with additional sedative agents, such as barbiturates or propofol [4]. Markers to identify this population of BZD-resistant patients may allow for earlier administration of a second GABA agonist or a different GABA agonist and ultimately avoid the time spent administering large doses of ineffective BZD that results in the escalation of the severity of the alcohol withdrawal. These patients may have prolonged or complicated hospital course, require ICU admission and, in many cases, endotracheal

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intubation. Thus, the clinical entity of RAW must be further defined in order to give clinicians a better understanding of the unexpectedly large sedative dosing required and the complicated clinical course that may be encountered when managing these patients.

A reliable and early predictor of the ultimate severity of AW has not been identified. Although some clinical data (including the presenting serum ethanol concentration) have been examined as predictive of a difficult clinical course, they have been unable to guide decision-making regarding pharmacotherapy [5]. This prospective observational study was designed to describe clinical findings, interval and cumulative diazepam dosing, need for additional sedatives, and hospital courses of patients with RAW and compare it with similarly presenting patients with NRAW.

METHODS

During a period of 6 months, this prospective observational study sequentially enrolled patients who presented to an urban hospital emergency department and were diagnosed with AW by the ED physician who used historical and clinical findings. Enrollment criteria required patients to have a ≥50 mg of intravenous diazepam (or equivalent benzodiazepine dosing) within the first hour of treatment to control their alcohol withdrawal related psychomotor agitation or to attempt to normalize irregular vital signs. The achievement of normal vital signs was used as a marker for effective AW treatment, as this generally indicates a decrease in sympathetic tone. A patient was considered to have abnormal vital signs if they had any indices exceeding a blood pressure (either systolic or diastolic) >140/90 mmHg, a pulse rate 100 beats/minute, a temperature >38°C (with no signs of concurrent infection), and a respiratory rate >18 breaths/minute. As there is no published data, the diazepam dose of 50 mg IV was chosen as inclusion criterion because this suggests that the patient is in moderate to severe alcohol withdrawal and would require medical admission rather than admission to a detoxification service.

All enrolled patients were evaluated six times during the first 24 hrs at specific intervals and followed-up daily throughout their hospital stay. Patients were excluded if, during their ED evaluation, other serious concurrent illnesses (such as subdural hematoma, sepsis, pneumonia, and other illnesses) were uncovered or if they were on medications (such as beta-adrenergic antagonists, calcium channel blockers, and other medications) that would obfuscate vital sign abnormalities. Although our population of AW patients has a low rate of abuse of sympathomimetic medications, toxicology screens for cocaine and amphetamines were not routinely obtained and therefore the presence of these drugs cannot be excluded.

Upon hospital admission the following information was obtained on all patients: demographic data, vital signs, admission ethanol level, time since last drink, and cumulative first hour benzodiazepine dose. Interval and cumulative doses of IV sedative medications with concurrent vital signs and subsequent complications were recorded at hours 1, 2, 3, 6, 12, and 24, with time 0 as the moment when the first dose of a sedative was given. Treatment decisions were left up to the individual clinicians. Although there was no formal AW management protocol in place, extensive education by the medical toxicology and critical care services created uniformly agreed-upon goals: the use of a loading dose of BZD (primarily diazepam) to attain somnolence with easy arousability and improvement of the patient's blood pressure and pulse abnormalities while maintaining adequate ventilation [6]. Sedation requirement was defined as the dose of medication deemed necessary by the clinician to achieve the desired effect (specifically, resolution of psychomotor agitation, vital sign normalization, etc.).

Patients were considered to have resistant alcohol withdrawal (RAW) if, at the discretion of the bedside physicians, a second class of sedative agent was added to the treatment regimen within the first 24 hours to control the AW syndrome or if unexplained vital signs abnormalities at 24 hours continued despite appropriate treatment with BZD alone. Patients were considered to have non-resistant alcohol withdrawal (NRAW) if their symptoms were controlled within 24 hours with BZD therapy alone.

The University's Institutional Review Board approved this study. Statistical analysis was performed using ANOVA with Scheffe correction for post-hoc testing to compare the interval and cumulative dosing of BZD administration. Calculations were determined using Statview (Abacus Concepts Inc., Berkeley CA). Proportions were compared with chi-square and Fisher's exact test and for comparison between medians quartile 95% confidence intervals were prepared using nonparametric technique in StatsDirect ver. 2.3.4 (StatsDirect Ltd. Chesire, U.K.). Significance was assigned to p values <0.05.

RESULTS

Twenty (20) patients met enrollment criteria (≥50 mg of intravenous diazepam in their first hour) during the 6-month study period. One patient eloped during the observation period and was subsequently excluded. No patients were excluded based on concurrent illness or medication use. Of the remaining 19 patients, four had normal vital signs at 24 hours and never received a second sedative agent. These four patients, with a median age of 46.5, were classified as having NRAW. Fifteen patients, with a median age of 42, had persistent otherwise unexplained abnormal vital signs at 24 hours despite BZD therapy or received a second IV sedative agent and were therefore classified as having RAW.

Analysis of the demographic and clinical information obtained at the time of enrollment did not distinguish RAW patients from NRAW patients (*Table 1*). All of the NRAW patients had normal vital signs by the end of the third hour (*Table 2*) after receiving a median cumulative dose of 132.5 mg of IV diazepam (95% C.I. 70–170, range 70–170 mg) (*Figure 1*). The actual and median interval and cumulative doses of diazepam for the NRAW

TABLE 1. Enrollment Indices (hour 1)

Group	Age	Sex	ETOH level (mg/dL)	Days since last drink?	Hypertensive >140/90 mmHg	Tachycardia >100 BPM*	Febrile >100.4 F	Tachypnea >18 BPM*	1st hour sedation (diazepam IV mg)
NRAW	45	m	0	unk	Yes	Yes	No	Yes	70
NRAW	75	m	unk	unk	Yes	No	No	No	50
NRAW	48	m	284	unk	No	Yes	Yes	Yes	70
NRAW	37	m	0	4 days	No	Yes	Yes	Yes	60
RAW	54	m	20	1 day	Yes	No	No	No	50
RAW	58	m	0	1 day	Yes	No	Yes	Yes	50
RAW	42	m	322	unk	No	Yes	No	Yes	60
RAW	63	m	13	1 day	No	Yes	No	Yes	50
RAW	35	m	unk	3 days	Yes	Yes	No	Yes	50
RAW	28	m	4	1 day	Yes	Yes	Yes	No	130
RAW	52	m	18	3 days	Yes	No	No	Yes	50
RAW	43	m	89	6 days	No	Yes	No	Yes	75
RAW	43	f	unk	1 day	Yes	Yes	Yes	Yes	80
RAW	28	m	260	unk	Yes	Yes	No	Yes	50
RAW	37	m	0	3 days	Yes	No	No	No	50
RAW	35	m	153	unk	No	Yes	No	No	50
RAW	40	m	0	unk	Yes	Yes	Yes	No	50
RAW	50	m	200	unk	Yes	Yes	Yes	Yes	50
RAW	32	m	0	unk	Yes	No	No	Yes	50

unk = unknown
**BPM = beats/breaths per minute*

patients demonstrates that these patients received fewer sedatives than their RAW counterparts (*Figure 1*). During their hospitalization, NRAW patients did not receive another class of sedative agent, did not require intubation, did not become hypotensive, and did not have any infectious complications.

The 15 RAW patients had substantially greater actual and median interval and cumulative doses of diazepam (*Figure 1*). Of these patients, 15 had abnormal vital signs at 3 hours despite receiving a median cumulative dose of 220 mg of IV diazepam (95% C.I. 110–310, range 60–440mg) (*Table 2*). Ten patients had persistent tachycardia or hypertension at 24 hours. The RAW group received significantly higher median interval dosing at 6 hours ($p = 0.018$) and at 12 hours ($p = 0.05$) (*Figure 1*). Similarly, the median cumulative doses differed at hours 6, 12, and 24 (where $p = 0.035$, 0.02 and 0.02 respectively) (*Figure 1*). During their hospitalization, 14/15 (93%) RAW patients received an additional sedative at various points during therapy, often an intravenous barbiturate (such as phenobarbital or pentobarbital) for control of psychomotor agitation or normalization of vital sign abnormalities (*Table 2*); 7 of these 14 (50%) patients required intubation for hypoventilation. Of the 15 RAW patients, 5 (33%) had an episode of hypotension, and 4 (27%) developed pneumonia.

Neither interval nor cumulative diazepam doses were statistically different at 1, 2, and 3 hours. There was a non-significant but large difference in the interval doses administered at 3 hours: NRAW patients received a median diazepam dose of 22.5 mg (range 0–80 mg) while RAW patients received a median of 100 mg (range 0–310 mg), (*Figure 1*). Also at the hour-3-time-interval, there was a large but non-significant change in the administered interval and cumulative dosing that consistently differentiated the RAW from the NRAW patients (*Figure 1*).

DISCUSSION

Many previous investigators advocated that patients with alcohol withdrawal receive "symptom-triggered therapy" with benzodiazepines (BZD) as a means of treating their vital sign abnormalities, treating psychomotor agitation, and preventing seizures [1,3,7]. This approach has the advantage of minimizing

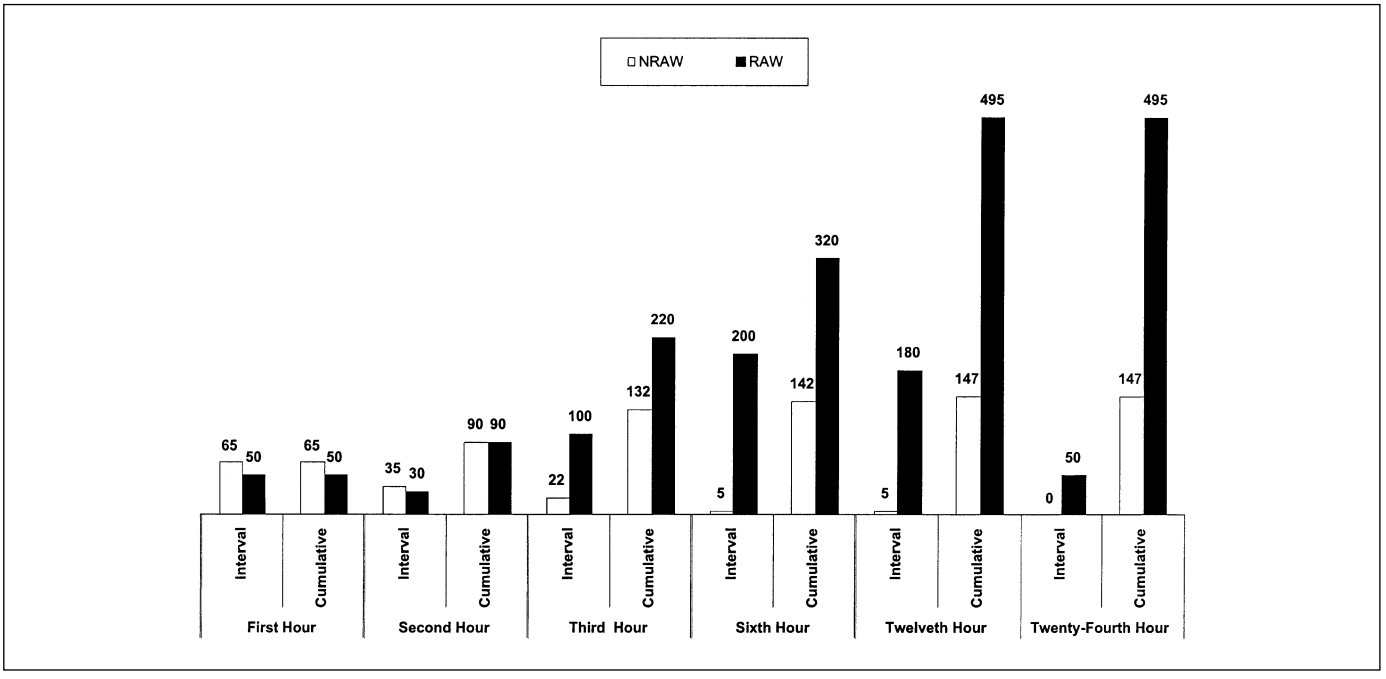

Figure 1. Median mg of Diazepam Doses

the total sedative dose, reducing the total duration or therapy, and virtually eliminating complications of under and over sedation [1,7].

It is well described that some heavy ethanol drinkers experience only mild AW upon cessation of drinking and some do not experience withdrawal at all [8]. Other patients, as in this investigation, require very large doses of intravenous BZD and other sedative agents to control their AW. The neurochemical basis for the development of the AW remains somewhat unclear, as does the basis for the resistance to standard therapies in some patients. Though likely multifactorial, the resistance to BZD may be due in part to a relative deficiency of gamma-aminobutyric acid (GABA), the primary endogenous inhibitory neurotransmitter in the central nervous system. Recent evidence also suggests that changes in the conformation of the GABA receptor reduce the sensitivity of the GABA receptors to BZDs [9]. Studies in short-sleep versus long-sleep mice suggest that genetic factors may be involved in these changes [10]. Alternatively, the enhancement of inhibitory tone by BZD may be insufficient to overcome an abundance of excitatory neurotransmitters (such as N-methyl-D-aspartate) that participate in the development of AW.

With no adequate published guidelines for the management of severe AW, the clinician must determine the optimal dosing regimen for the BZDs and to determine whether or not they are achieving the desired effect. In situations requiring the addition of another sedative agent to the withdrawal therapy, our institution relies on intravenous barbiturates as the second line of therapy. Medications that simply normalize a patient's signs of AW such as central alpha$_2$ agonist (e.g. clonidine, dexmedetomidine) and beta adrenergic antagonists are not used because they may obscure signs of continued AW and the need for additional sedation.

We have found that there is a distinct subgroup of patients with RAW in whom typical therapeutic management of their withdrawal with BZD does not have the desired effects. In this study, we were not able to discern overt differences in admission indices that would allow clinicians to distinguish between patients who would ultimately develop RAW. During the first day of treatment, the RAW patients received continued escalating doses of BZD during each time interval, and most received the addition of a second class of sedative agent.

At 3 hours, all of the patients in the NRAW group had normalization of their vital signs with a cumulative diazepam dose less than 200 mg of IV diazepam (median dose 132.5 mg). At the same time, all 15 RAW patients had persistent vital sign abnormalities of AW, despite 9 of them receiving a cumulative dose ranging from 220–440 mg of IV diazepam. Although not statistically significant, all of these patients in the study who received a cumulative dose of 200 mg of IV diazepam at 3 hours for control of their AW syndrome were in the RAW group; this BZD requirement might be an early prognostic indicator for having RAW. Although all patients with AW should be treated and dispositioned in a clinically appropriate manner, there may be a unique population at risk for complications and high dose sedative requirements. As no previous study has identified or described RAW patients, we present this dose of diazepam and time frame as a potential indicator that such patients should be aggressively treated and closely monitored in an intensive care setting because their withdrawal may be more severe and complicated than other AW patients. This requires validation and refinement in a larger study group.

TABLE 2. Vital Signs: blood pressure and pulse at the end of each interval

	1h	2h	3h	6h	12h	24h
NRAW	170/90, 112	130/74, 80 (A,2)	130/74, 80	130/74, 80	130/74, 80	130/74, 80
NRAW	170/92, 76	140/85, 90	135/90, 90	110/75, 80	110/75, 80 (A,12)	110/85, 85
NRAW	127/60, 103	107/64, 81	105/62, 88	100/60, 80	100/60, 82 (A,12)	120/85, 90
NRAW	140/70, 100	142/90, 130	130/80, 81	130/80, 81	130/80, 81	130/80, 81 (A.24)
Number with vital sign abnormality	4/4	1/4	0/4	0/4	0/4	0/4
RAW	144/83, 94	155/85, 96	154/100, 98	152/110, 88	158/104, 110	140/85, 116 (B,17) (C-20)
RAW	154/72, 90	124/63, 115	120/65, 112	116/60, 105	109/56, 90 (C,12)	103/56, 85
RAW	132/70, 110	172/98, 123	157/106, 130	167/90, 118	115/72, 115	115/72, 115
RAW	133/75, 129	140/63, 112	134/68, 110	136/78, 106	157/83, 114	81/46, 112 (C,17)
RAW	141/74, 117	141/84, 121	128/61, 121	133/92, 101	126/78, 104	114/42, 113 (B,16)
RAW	160/100, 140	160/100, 135	140/89, 106 (C,3)	132/87, 114	89/60, 103	99/70, 89
RAW	150/98, 93	150/80, 90	168/89, 105	182/98, 135	138/78, 80 (B,8)	128/66, 104
RAW	134/90, 120	130/100, 118	130/100, 118	149/92, 116 (B,4)	156/90, 85 (C,8)	98/58, 103
RAW	142/86, 104	140/74, 148	144/85, 123	128/78, 81	108/70, 92	134/72, 106 (B,24)
RAW	150/60, 152	160/60, 140	150/60, 125	150/70, 130 (B,6)	137/84, 114	150/84, 116
RAW	156/92, 80	160/92, 110 (C,2)	160/80, 110	150/85, 100	140/68, 95	140/60, 90
RAW	100/70, 100	125/70, 120	130/70, 140	120/70, 100	120/70, 95 (C,12)	120/70, 95
RAW	160/115, 125	147/76, 91	160/86, 95	134/78, 134	157/89, 110 (C,12)	157/89, 110
RAW	200/100, 120	200/90, 130 (B,2)	190/90, 130	176/86, 110	160/82, 100	160/82, 100
RAW	142/92, 96	117/76, 89	154/103, 124	132/82, 109 (B,6)	122/82, 117	120/80, 90
Number with vital sign abnormality	15/15	13/15	15/15	14/15	10/15	10/15

Key: (#) indicates hour where additional sedative was administered
Additional sedatives: A—chlordiazepoxide, B—phenobarbital, C—pentobarbital

LIMITATIONS

Because of the severity of illness at presentation and continuing need for sedative agents, our study is observationally descriptive in that we were unable to obtain a detailed history from the RAW patients in order to contrast the groups' drinking histories (years of drinking, amount of daily ethanol intake, days in a row of alcohol exposure prior to ED arrival), number of previous AW episodes, previous exposure to high dose benzodiazepines, and nutritional status—all of which may have been useful to distinguish these groups.

Although we found a statistical difference in the interval and cumulative doses, the number of patients with NRAW was small and limited the statistical analysis. This is probably due to the inclusion criterion requiring the administration of 50 mg diazepam in the first hour; we likely have excluded the majority of patients with NRAW.

As this is the first study to identify this RAW group, our goal was to observe and describe, not to formulate treatment. Therefore, we did not compare protocols to attempt to standardize the diagnosis and pharmacotherapy of alcohol withdrawal in these patients or to alter the institutional standard of therapy. Hypothetically, this may have led to which group a patient was ultimately considered to belong to. The use of a standardized scoring system (to assist in the decision to administer additional sedatives or to alter the pharmacotherapeutic regimen) was similarly not part of this study. Scoring systems, such as CIWA-Ar, have not been applied to patients who have life-threatening AW. It is primarily used to describe patients with mild-moderate withdrawal, most of whom only require treatment with oral benzodiazepines.

CONCLUSION

There exists a sub-population of patients with resistant alcohol withdrawal (RAW) that require large doses of multiple sedative medications to control their symptoms for the first 24 hours. The doses of BZDs rapidly escalate and RAW patients often require the addition of other GABA agonists for symptom control, and their hospital courses are often complicated. There is no clear early indicator to determine which patients will have RAW.

Although there is no validated early marker to identify this resistant group, perhaps the combination of continued abnormal vital signs (despite BZD therapy) coupled with patients requiring diazepam IV >200 mg cumulative dose at 3 hours may be at high risk for having resistant alcohol withdrawal (RAW). Further study is required to confirm our findings.

The authors have no potential financial conflicts of interest to report.

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