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Pilot Study of the Effect of Lipophilic vs. Hydrophilic Beta-Adrenergic Blockers Being Taken at Time of Intracardiac Defibrillator Discharge on Subsequent PTSD Symptoms

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1. Introduction

Posttraumatic Stress Disorder (PTSD) is a mental disorder that may result from exposure to an extreme, psychologically traumatic event. A cardinal feature of PTSD is strong, durable, intrusive, and distressing memories of the event, which in some cases may persist for a lifetime (Orr, Pitman, Lasko, and Herz, 1993). A number of endogenously released or exogenously administered stress-related hormones, including epinephrine and cortisol (corticosterone in rodents), have been found to strengthen memory consolidation in laboratory experiments (McGaugh, 2013; Roozendaal and McGaugh, 2011). The intense fear, helplessness, and/or horror in response to the traumatic event typically experienced by persons who go on to develop PTSD are likely accompanied by the endogenous release of stress hormones. We have hypothesized that such hormones, by overly strengthening consolidation of the memory of the traumatic event, may be involved in the pathogenesis of

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DISCLOSURES

The remaining authors have no disclosures.

PTSD, reflecting an overshoot of an ordinarily adaptive mechanism (Pitman, 1989). Systemic administration of the lipophilic β -adrenergic blockers propranolol and metoprolol, which are capable of crossing the blood-brain barrier, has been found to oppose the potentiation of memory consolidation by stress (Cahill, Pham, and Setlow, 2000; Cahill, Prins, Weber, and McGaugh, 1994; O'Carroll, Drysdale, Cahill, Shajahan, and Ebmeier, 1999) and stress hormones (McGaugh, 2013; Roozendaal, Okuda, Van der Zee, and McGaugh, 2006) through a final common pathway. In contrast, systemic hydrophilic β -blockers such as sotalol and nadolol, which do not cross the blood-brain barrier, typically have been found not to exert such an effect (Introini-Collison and Baratti, 1986; Robinson and Franklin, 2007).

If the above hypothesized pathogenic model of PTSD is valid, then the administration of lipophilic β -blockers following the occurrence of a traumatic event might reduce the likelihood of subsequent PTSD by blocking stress-induced overconsolidation of the traumatic memory. This has been investigated in several studies that have employed propranolol, with positive (Vaiva, Ducrocq, Jezequel, Averland, Lestavel, Brunet, and Marmar, 2003), negative (Stein, Kerridge, Dimsdale, and Hoyt, 2007), and mixed (Hoge, Worthington, Nagurney, Chang, Kay, Feterowski, Katzman, Goetz, Rosasco, Lasko, Zusman, Pollack, Orr, and Pitman, 2012; Krauseneck, Padberg, Roozendaal, Grathwohl, Weis, Hauer, Kaufmann, Schmoedel, and Schelling, 2010; Nugent, Christopher, Crow, Browne, Ostrowski, and Delahanty, 2010; Pitman, Sanders, Zusman, Healy, Cheema, Lasko, Cahill, and Orr, 2002) results. One possible reason for failure to observe a PTSD preventive effect of propranolol is the delay between the traumatic event's occurrence and the administration of the drug, which in some of the above studies was a day or longer. The susceptibility of memory consolidation to noradrenergic influences, which propranolol antagonizes, has been shown to be restricted to a time window, which may only consist of several hours (Gazarini, Stern, Carobrez, and Bertoglio, 2013). It is possible that in the above studies, the propranolol exerted its effect too late to significantly oppose excessive memory consolidation induced by the traumatic stress, thereby precluding a valid test of the hypothesis. It is possible that propranolol, or other lipophilic β -blockers, administered sooner would be more effective. Even more effective might be β -blockers that are already on board at the time the traumatic event.

Intracardiac defibrillators (ICDs) have been successfully surgically implanted in humans since 1980. Recent models allow for office-based, subcutaneous implantations. The battery-powered ICD monitors heart rhythms and automatically discharges an electrical impulse (shock) to the heart when an abnormal, potentially fatal rhythm is detected. These devices have been shown to decrease mortality from cardiac causes and have been prescribed for millions of patients with histories of potentially fatal arrhythmias, myocardial infarction, congestive heart failure, and other cardiac risk factors (Al-Khatib, Hellkamp, Bardy, Hammill, Hall, Mark, Anstrom, Curtis, Al-Khalidi, Curtis, Heidenreich, Peterson, Sanders, Clapp-Channing, Lee, and Moss, 2013).

ICD discharges are often experienced as highly stressful, and they have been found to be associated with subsequent PTSD symptoms (Sears, Jr. and Conti, 2003). Some patients have described them in dramatic terms, e.g., "like being kicked in the chest by a mule."

Syncope or other brief physical incapacitation may even occur. In addition to the upsetting nature of the unpredictable, uncontrollable discharge itself, the fact that an ICD discharge has occurred may alert the patient to the possibility that a life-threatening event has taken place, or even worse is still taking place, in their heart, thereby increasing the traumatic psychological effect. Sometimes a series of ICD discharges, or “storms,” may occur, multiplying the trauma. ICDs may also discharge spuriously, i.e., in the absence of an arrhythmia, and the patient may not know the difference. Both warranted and spurious discharges have been characterized as stressful in cardiac patients’ quality of life narratives (Ford, Sears, Shea, and Cahill, 2013).

Beta-blockers (including lipophilic drugs such as propranolol, metoprolol, and carvedilol, and hydrophilic drugs such as atenolol and sotalol) are part of the preventive cardiology armamentarium. Most patients with ICDs are prescribed one or more lipophilic or hydrophilic β -blockers. Because such patients would already be taking β -blockers at the time an ICD discharge occurred, they may offer an opportunity to test the putative, central PTSD preventive effect of lipophilic β -blockers that is free of the problem of a delay between the traumatic event’s occurrence and the administration of drug. It is possible that the peripheral effects of β -blockers alone could confer prevention against PTSD, e.g., according to a James-Lange type mechanism, in which diminished perception of peripheral physiological arousal due to the drug reduces fear. Including patients who were taking hydrophilic β -blockers at the time of ICD discharge in the scientific design provides a control for this possibility, given that the anti-adrenergic effects of hydrophilic β -blockers are at least as great as those of lipophilic β -blockers (Kardos, Long, Bryant, Singh, Sleight, and Casadei, 1998).

With the above limitations in mind, the present, retrospective pilot study evaluated PTSD symptoms related to an ICD discharge event that occurred in cardiac patients who were taking either prescribed lipophilic or hydrophilic β -blockers at the time of the discharge.

2. Methods

2.1 Subjects

Subjects comprised a convenience sample of 18 male outpatients. (Too few female subjects could be recruited to form an analyzable group.) Each subject had been seen for a visit at least once at the Massachusetts General Hospital (MGH) Cardiac Arrhythmia Clinic during the year preceding the study, and each had experienced at least one ICD discharge sometime in the past, excluding “test shocks” (in which the device was interrogated within a controlled hospital setting in a predictable fashion expected by the patient). In order for a patient to be included, it was necessary both that the medical records documented that the patient had been prescribed a β -blocker at the time of the “index” ICD discharge, and that the patient confirmed that they were taking the medication at the time.

Prior to contacting subject candidates, the electronic medical record, including entries from all disciplines including psychiatry, was reviewed for potentially excluding factors. All subjects had been followed at the MGH for at least three years. All had been screened for psychiatric disorders using standard questions, the results of which were entered in the

record. The exclusion criteria included: age <18 years; any pre-existing DSM-IV (American Psychiatric Association, 1994) Axis I mental disorder, including PTSD from another traumatic event, and substance abuse or dependence; or current medical illness that contraindicated participation (e.g., asthma). As shown in Table 1, two patients (both in the lipophilic β -blocker group) were taking benzodiazepine anxiolytics at the time of the index ICD discharge (DR and VO in Table 1).

2.2 Institutional Review Board Approval and Informed Consent

Partners Healthcare Institutional Review Board (IRB) approval was obtained to 1) conduct chart reviews in order to identify eligible subject candidates, 2) mail a postcard requesting eligible candidates to contact the investigators if interested in participation, and 3) conduct telephone interviews of subjects who indicated an interest, including administration of a PTSD symptom questionnaire. After a full explanation of the study's procedures, written informed consent was obtained from all subjects on a form approved by the IRB.

2.3 Psychometric Instrument

The Post-Traumatic Stress Disorder Check List (PCL) has been highly validated (Wilkins, Lang, and Norman, 2011), including in cardiac patients (e.g. Prudente et al 2006). The correlation between total PCL score and total score on the Clinician-Administered PTSD Scale has been reported at $r = 0.80$ among several cohorts of medical patients. (Wilkins, Lang, and Norman, 2011). The PCL is a self-report rating scale that comprises 17 items corresponding to the 17 DSM-IV diagnostic criteria for PTSD. A Likert-type scale (1 to 5) is used by the patient to report how much they have been bothered by each PTSD symptom during the past month, with 1 designating "not at all," and 5 designating "extremely." For this study, the PCL-Specific (PCL-S) version) (Weathers F., Litz, Huska, and Keane, 1994) was used. This version pertains to a specific traumatic event, in this case the ICD discharge. If a patient had experienced more than one ICD discharge, they were asked to identify the one that they remembered as having been most stressful for them, and the PCL-S was administered with reference to that ("index") event.

2.4 Drug Lipo- vs. Hydrophilicity

Beta-blockers were classified as either lipophilic or hydrophilic according to guidelines of the Task Force on Beta Blockers of the European Cardiology Society (Lopez-Sendon, Swedberg, McMurray, Tamargo, Maggioni, Dargie, Tendera, Waagstein, Kjekshus, Lechat, and Torp-Pedersen, 2004). Brain mitochondrial delivery is strongly influenced by lipophilicity (Durazo, Kadam, Drechsel, Patel, and Kompella, 2011). In this study, patients who were taking metoprolol, propranolol, or carvedilol at the time of the index ICD discharge were classified into the Lipophilic group. Patients who were taking atenolol or sotalol were classified into the Hydrophilic group.

3. Results

Table 1 presents information on individual subjects, including age, time elapsed since the index ICD discharge, diagnoses, the β -blocker and other medications the patient was taking at the time of the index ICD discharge, and PCL-S score (past month). Table 2 presents

group mean ages, times elapsed since the index ICD discharge, and PCL-S scores. It will be seen that there were no significant group differences in age or time elapsed. The group difference in PCL scores approached but did not achieve statistical significance: one-tailed $p=0.07$. There were no significant correlations between PCL score and either age or time elapsed: $r=-0.23$, $p=0.37$ and $r=-0.29$, $p=.23$ respectively.

4. Discussion

In the present retrospective pilot study, patients who experienced an ICD discharge while they were taking a lipophilic β -blocker at the time showed a trend toward reporting less severe PTSD symptoms related to the discharge event during the month prior to evaluation, compared to patients who had been taking a hydrophilic β -blocker. Taking into account that, by virtue of the PCL-S scale construction, a patient with no PTSD symptoms would have a score of 17, the PTSD symptoms of patients on lipophilic β -blockers were 35% less severe than those who were on hydrophilic β -blockers at the time of the ICD discharge (effect size $g=0.64$). Because both types of β -blockers produce comparable peripheral anti-adrenergic effects, this group difference potentially implicates a central β -adrenergic mechanism in the pathogenesis of PTSD symptoms. It is possible that the benzodiazepines being taken by two subjects in the lipophilic group partially accounted for the group difference in PCL-S scores. However, their use of benzodiazepines was low-dose and long-standing. Moreover, the existing literature does not support the efficacy of this drug class for PTSD. [Ravindran and Stein, 2010]

The present results provide tentative evidence in support of the theories that excessive endogenous stress hormones released in reaction to the traumatic event increase PTSD risk by potentiating consolidation of the memory of the traumatic event through a β -adrenergic mechanism, and that central β -adrenergic blockade may reduce this effect. Although alternate brain mechanisms cannot be ruled out, none has the extensive body of preclinical research evidence to support it.

The limitations of the present study are numerous. The study was retrospective in nature. Sample sizes were small, and participants were not systematically ascertained. Due to budgetary limitations, assessment of PTSD symptoms relied on subjects' self-reports on a questionnaire administered over the telephone. Many subjects had experienced more than one ICD discharge in the past, but they were asked to focus on psychological symptoms associated with a single "index" discharge, which may have occurred years earlier. Some subjects may have had difficulty separating the effects of that discharge from others they had experienced. Some ICD discharge events were unitary, whereas others were multiple (so-called storms). It was not feasible to retrospectively quantify the severity of the index ICD discharge event, much less match groups for this variable, nor for other potentially confounding variables such as cardiac and other medical diagnoses, and other medication use, both at the time of the ICD discharge and at the assessment. Other authors have called attention to the potentially different effects of more versus less painful shocks, and the need to quantify psychophysiologic responses to shocks, e.g., via electromyography in an attempt to establish causality between physical pain and resulting psychological distress (Baumert, Schmitt, and Ladwig, 2006), but the retrospective nature of our study precluded this.

Additionally, the analysis of group differences may have been confounded by non-random assignment of subjects to type of beta-blocker. Although hydrophilic and lipophilic beta blockers have overlapping indications, they may also have distinct indications, with sotalol (hydrophilic) being slightly more indicated for cardiac arrhythmia, carvedilol and extended release metoprolol (both lipophilic) having greater efficacy in congestive heart failure than the hydrophilic agents, and both lipophilic (metoprolol, propranolol) and hydrophilic (atenolol) agents being indicated for myocardial infarction. In addition, individual factors in the decision to prescribe a given drug to a given patient may dictate deviations from the above guideline. For example, two subjects with congestive heart failure in our sample had been prescribed sotalol.

The adverse psychological impact of ICDs has been documented in a number of depression, anxiety, and cardiac quality of life studies. In addition to problem posed by this psychiatric morbidity itself, the presence of PTSD symptoms in ICD patients is associated with a higher risk of death, even after adjusting for key medical factors (Ladwig, Baumert, Marten-Mittag, Kolb, Zrenner, and Schmitt, 2008). Therefore, the search for effective interventions to prevent PTSD in cardiac patients with ICDs is of clinical importance. Tailored cognitive behavioral therapy has been used to assist patients in adapting to ICDs (Irvine, Firestone, Ong, Cribbie, Dorian, Harris, Ritvo, Katz, Newman, Cameron, Johnson, Bilanovic, Hill, O'Donnell, and Sears S Jr, 2011). The present results suggest that a secondary pharmacological preventive approach to this problem may also be promising.

The present results should properly be viewed as offering preliminary data supporting the performance of further, better controlled, studies with designs that attempt to address the limitations discussed above. Improvements in future work could also include recruiting an adequate number of women, given the finding of Krauseneck and colleagues (2010) that beta blockade may have particular efficacy for PTSD prevention among women exposed to ICD shocks and other cardiac traumas.

A next logical step would be a prospective study of patients newly provided ICD devices and prescribed the treating cardiologist's β -blocker of choice. Patients could be monitored for the occurrence of an ICD shock and then comprehensively psychiatrically evaluated in person over a series of visits. Should the results of such a study support the superiority of lipophilic over hydrophilic β -blockers in preventing shock-related psychiatric morbidity, a next step might be a prospective controlled study that randomly assigned patients to be prescribed ICDs to either a lipophilic or hydrophilic β -blocker, other (e.g., cardiac) considerations permitting. Additional studies could compare various lipophilic β -blockers with each other, or even try more promising drugs that may emerge in the future with effects on memory consolidation and reconsolidation.

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Table 1

Individual Subject Information

Initials	Age ^a	Months Elapsed ^b	Diagnoses ^c	β-Blocker ^{c,d}	Other Medications ^e	PCL ^{a,e}
AB	81	10	Idiopathic dilated cardiomyopathy	Carvedilol	Amiodarone, Digoxin, Enalapril, Furosemide Potassium, Vasotec, Warfarin	2
CC	65	62	Ischemic cardiomyopathy	Metoprolol	Digoxin, Lisinopril, Spironolactone, Warfarin	25
DC	78	84	Ischemic cardiomyopathy	Metoprolol	Azithromycin, Bumetanide, Ceftriaxone, Colchicine, Digoxin, Hydrocodone, Losartan, Simvastatin, Spironolactone, Vitamin E, Warfarin	0
DM	76	25	Ischemic cardiomyopathy	Carvedilol	Acetylsalicylic acid, Allopurinol, Colchicine, Digoxin, Fenofibrate, Furosemide, Glipizide, Lantus, Monopril, Sildenafil, Simvastatin, Terazosin, Warfarin	21
DR	80	6	Idiopathic dilated cardiomyopathy	Carvedilol	Digoxin, Folic Acid, Furosemide, Ibuprofen, Lisinopril, Lorezapam, Omeprazole, Simvastatin, Spironolactone	44
EFi	82	23	Ischemic cardiomyopathy	Metoprolol	Atorvastatin, Hydrochlorothiazide, Warfarin	0
EFo	63	23	Ischemic cardiomyopathy	Carvedilol	Atorvastatin, Digoxin, Furosemide, Glipizide, Lisinopril, Metformin, Niacin, Spironolactone, Warfarin	21
EM	58	1	Ischemic cardiomyopathy	Atenolol	Acetylsalicylic acid, Calcium/Vitamin D, Digoxin, Furosemide, Lipitor, Lisinopril, Warfarin	29
GH	33	92	Familial hypertrophic cardiomyopathy	Metoprolol	Amiodarone	0
JM	71	70	Ischemic cardiomyopathy	Atenolol	Acetylsalicylic acid, Amiodipine, Atorvastatin, Ipratropium bromide, Lisinopril, Metformin, Nicotine patch	40
NM	60	47	Idiopathic cardiomyopathy	Propranolol	Acetylsalicylic acid, Captopril, Digoxin, Dofetilide, Furosemide, KCL, Warfarin	35
PG	47	37	Non ischemic (idiopathic) cardiomyopathy	Sotalol	Aldactone, Warfarin	18
PW	31	13	Non ischemic (idiopathic) cardiomyopathy	Sotalol	Lisinopril	43
RM	71	14	Congestive heart failure	Atenolol	Allopurinol, Bumex, Digoxin, Glipizide Lovastatin, Losartan, Sitagliptin,	20
RP	58	13	Dilated cardiomyopathy, cause uncertain (non-ischemic)	Metoprolol	Digoxin, Warfarin	45
SC	76	59	Ischemic cardiomyopathy	Carvedilol	Acetylsalicylic acid, Losartan, Multi Vitamin	24
TS	62	49	Ischemic cardiomyopathy	Atenolol	Acetylsalicylic acid, Magnesium oxide	24
VO	78	6	Ischemic cardiomyopathy	Metoprolol	Acetylsalicylic acid, Flomax, Flurazepam, Fluticasone propionate, Gemfibrozil, Isosorbide, Mononitrate, Niacin Extended Release, Omeprazole, Synthroid, Tiotropium bromide	10

Notes:

^a At time of evaluation

^b Months elapsed from index AICD discharge to time of evaluation

^c At time of index discharge

^d Lipophilic β -blockers drugs (n=12): carvedilol, metoprolol, propranolol; hydrophilic β -blockers (n=6): atenolol, sotalol

^e PCL= PTSD Checklist Score

Table 2

Group Means and Standard Deviations

	On Lipophilic β-Blocker	On Hydrophilic β-Blocker	<i>t</i>	<i>df</i>	<i>p</i>
<i>n</i>	12	6			
Age (yrs.)	69.1 (14.7)	56.6 (15.4)	-1.7	16	0.11
Time elapsed since index AICD discharge (mos.)	36.5 (30.3)	30.7 (26.1)	-0.4	16	0.69
PCL-S ^c	35.9 (16.8)	46.0 (10.4)	1.6 ^a	14.9	0.07 ^b

Notes:

Numbers in parentheses are standard deviations

^a *t*-test for unequal variances

^b One-tailed, Hedge's *g*=0.64

^c PTSD Checklist-Specific Score, range 17–85