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Effects of early albuterol (salbutamol) administration on the development of posttraumatic stress symptoms

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Abstract

The present study examined whether use of albuterol within hours of a motor vehicle accident (MVA) impacted subsequent posttraumatic stress symptoms (PTSS). Participants receiving albuterol had less severe overall PTSS and hyperarousal symptoms at 6-weeks and less severe reexperiencing symptoms at 1-year post-MVA than those who did not receive albuterol.

Keywords

β_2-adrenergic receptor agonist; pharmacologic intervention; motor vehicle accident

1. Introduction

Studies suggesting beneficial effects of early drug administration at preventing the development of posttraumatic stress disorder (PTSD: Schelling et al., 2001; Pitman et al., 2002) have, for the most part, hypothesized mechanisms of drug action involving interfering with consolidation or retrieval of traumatic memories (Pitman and Delahanty, 2005). Albuterol (Salbutamol: International Nonproprietary Name) is a β_2-adrenergic receptor agonist often used to treat acute asthma attacks and respiratory failure or insufficiency after an injury (Bellenir, 2006). Albuterol rapidly crosses the blood brain barrier (Caccia and Fong, 1983), and inhalation of a low dose of nebulized albuterol enhances while a high dose interferes with avoidance learning in rats (Elias et al., 2004). According to the widely-accepted two-process theory of avoidance learning, conditioned fear is presumed to be the basis for learned avoidance (McAllister and McAllister, 1991). Albuterol may impact posttraumatic stress symptoms (PTSS) by interfering with initial fear responses. The present

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study represents a post-hoc examination of the extent to which albuterol, administered in hospital following a motor vehicle accident (MVA), is associated with subsequent PTSS.

2. Methods

2.1. Participants

Participants were 375 (223 males and 152 females, mean age and SD = 38.3 ± 16.2) years) MVA victims who were admitted to the level 1 trauma center of one of two community hospitals. Exclusion criteria included scoring below a 14 on the Glasgow Coma Scale (Teasdale and Jennett, 1974) and/or having psychotic or bipolar disorders (via medical chart report). 116 participants had positive toxicology screens (100 alcohol, 13 cocaine, 7 opioids, 4 cannabis, 3 benzodiazepine, and 1 amphetamine). Excluding these participants did not impact results, so positive toxicology screens did not serve as exclusionary criteria. According to patients' charts, 38 participants received albuterol in hospital within 25 hours of admission, and we were able to obtain detailed information regarding albuterol administration (dose and timing of medication administration) for 20 participants. Participants received 2, 3, or an unspecified number of puffs of albuterol through an aerosol or inhaler every 4 or 6 hours or as needed except one who received a 4 mg tablet twice a day. The first administration of albuterol occurred between 3 and 25 hours after admission, and duration of administration ranged from 0 (administered only once) to 197 hours (mean = 64.7). 255 participants completed the 6-week follow-up assessment, and 182 completed the 1-year follow-up. Completers and non-completers did not differ in terms of injury severity scores (ISS), or in-hospital albuterol use; however, non-completers were more likely to be male [$\chi^2 = 4.7$, $P = 0.03$; $\chi^2 = 6.62$, $P = 0.01$], non-White [$\chi^2 = 11.1$, $P = 0.001$; $\chi^2 = 7.56$, $P = 0.006$], and younger [$t(370) = 2.03$, $P = 0.04$].

2.2. Procedure

The present procedures were approved by the human subjects review boards of Kent State University, Summa Health System, and Akron General Medical Center. As part of the written consent process, participants gave permission to have their medical charts reviewed for the recording of medications received in hospital, injuries suffered, toxicology screening results, heart rates measured during Emergency Medical Service transport and in the emergency room (ER), and medical history. In addition, participants completed the Impact of Event Scale –Revised (IES-R: Weiss, 2004). Six weeks and 1 year later, a clinical psychology graduate student administered the Clinician Administered PTSD Scale (CAPS: Blake et al., 1990) at participants' homes. Participants were paid $25 for completing each assessment.

2.3. Measures

The IES-R is a 22-item questionnaire designed to measure levels of distress stemming from PTSS (Weiss, 2004). The CAPS is a structured interview designed to assess the frequency and intensity of 17 current and past PTSS. The injury severity scale (ISS: Baker et al., 1974) is an objective index of injury severity.

2.4. Data Analyses

CAPS scores were square-root transformed to normalize the positively skewed distributions. Differences between groups in 6-week and 1-year CAPS scores were examined with *t*-tests. Welch's *t* was computed when significant heterogeneity of variance between groups was found. Subsequent ANCOVAs were conducted to determine whether differences between groups persisted after covarying for confounding variables.

3. Results

The albuterol group had significantly higher ISSs [12.7±9.7 vs. 6.7±6.7; Welch's $t(39) = 3.78$, $P = 0.001$], a longer hospital stay [105.9±91.1 vs. 69.8±78.0 hours; $t(362) = 2.65$, $P = 0.008$], and a greater proportion of patients reporting a history of asthma (6 out of 38 albuterol vs. 13 out of 337 no-albuterol participants; $P = 0.007$) and psychiatric disorders (depression, anxiety disorders other than PTSD, and/or substance use disorders reported in the charts), $\chi^2(1, N = 375) = 7.0$, $P = 0.008$. With respect to type of injuries, there was a higher rate of rib fracture and pneumothorax in the albuterol group, $\chi^2 = 26.0$, $P < 0.001$. In addition, the albuterol group demonstrated a trend towards being older [42.4±15.4 vs. 37.8±16.2; $t(370) = 1.68$, $P = 0.10$] than the no-albuterol group. Groups did not differ in terms of sex, race, in-hospital IES-R scores, heart rates measured during transport or upon admission to the ER, past PTSD diagnoses measured by the CAPS (3 albuterol vs. 42 non-albuterol participants had past PTSD), or use of β-blockers (1 albuterol vs. 15 non-albuterol participants were on β-blockers). Given observed group differences, we included ISS, presence versus absence of rib fracture/pneumothorax, a history of psychiatric disorders, and age in the subsequent ANCOVAs as covariates. Length of hospital stay was not included as a covariate because of its conceptual and statistical overlap with ISS ($r = 0.48$, $P < 0.001$). Effects of asthma status on CAPS scores were examined separately.

Results of *t*-tests comparing the CAPS scores between the groups are presented in Table 1. The CAPS total, re-experiencing (at 6-weeks and 1-year), and hyperarousal (at 6-weeks) scores were significantly lower for the albuterol group than the no-albuterol group. No patients in the albuterol group subsequently developed PTSD, whereas 27 and 15 patients in the non-albuterol group met PTSD diagnostic criteria at 6-weeks and 1-year post-MVA. Group differences in diagnostic status were not statistically significant.

Subsequent ANCOVAs covarying for the impact of age, gender, race, ISS, rib fracture/pneumothorax, and psychiatric history did not change the results. The albuterol group continued to have lower 6-week CAPS total, re-experiencing, and hyperarousal scores [$F(1, 247) = 6.0$, 3.7, and 8.4, $P = 0.02$, 0.06, and 0.004, respectively] and lower 1-year re-experiencing [$F(1, 175) = 4.2$, $P = 0.04$] scores.

To examine whether albuterol use was masking an effect of asthma, we compared CAPS scores of non-albuterol participants with asthma (n=13 at 6-weeks, 9 at 1-year) to the albuterol group. Results of *t*-tests showed that the albuterol group had lower 6-week CAPS total, reexperiencing, hyperarousal, and avoidance [$t(34) = -3.3$, -2.7, -2.5, and -2.4, $P = 0.003$, 0.01, 0.02, and 0.02, respectively] and 1-year reexperiencing [$t(27) = -2.3$, $P = 0.03$] scores compared to the non-albuterol participants with asthma.

Because beta-adrenergic agonism may reduce trauma-related dreams (McAinsh and Cruickshank, 1990), we also examined group differences in the number of participants who endorsed CAPS item B-2 that measures trauma-related nightmares. At 6-weeks post-MVA, no participant in the albuterol group endorsed the item whereas 53 participants in the non-albuterol group endorsed the item ($P = 0.006$). At 1-year post-MVA, no participants in the albuterol group endorsed the item, but 10 participants in the non-albuterol group reported trauma-related nightmares ($P = 0.61$).

4. Discussion

Results of the present exploratory analyses suggest that albuterol administered soon after an MVA was associated with lower subsequent PTSS. Prior studies have suggested an inverted-U shaped relationship between dose of post-training epinephrine (an adrenergic receptor agonist) and memory performance (McGaugh, 1989). Albuterol's dose-dependent effects on

avoidance learning (Elias et al., 2004) in animal models seem to be consistent with this inverted-U shaped relationship. Perhaps administration of albuterol in this study resulted in memory effects similar to those that would be observed following administration of a high dose of albuterol in this hypothetical inverted-U shaped relationship. More specifically, albuterol might have interfered with early fear conditioning and consolidation/reconsolidation, thus decreasing one's risk for the development of PTSS (Pitman et al., 2002).

With regard to limitations of this study, these data represent a post-hoc exploration, and the parent study was not designed to test the efficacy of in-hospital albuterol administration. Groups were not randomized, and potential confounds such as use of β-blockers and effects of substances with sympathomimetic properties were not controlled. It is possible that a third variable accounts for the differences between groups. An additional limitation is that participants were MVA patients with mild PTSS, and it is unclear whether the present findings would be generalizable to victims of other types of trauma. Replication in a larger, randomized trial is necessary to increase confidence in the efficacy of early albuterol administration at preventing/reducing PTSS.

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Table 1

6-Week and 1-Year Post-Motor Vehicle Accident CAPS Scores.

	Albuterol	**No Albuterol**	***t or* Welch's *t***	***P***
6 Weeks	(n = 23)	(n = 232)		
Total CAPS Score	14.5 ± 10.6	26.8 ± 21.4	−3.67	0.001
Reexperiencing	2.3 ± 3.2	6.8 ± 7.5	−3.73	0.001
Hyperarousal	5.3 ± 6.1	9.8 ± 8.0	−2.93	0.007
Avoidance	6.9 ± 5.1	10.2 ± 9.9	−1.33	0.18
1 Year	(n = 20)	(n = 162)		
Total CAPS Score	11.2 ± 7.8	19.4 ± 19.9	−1.70	0.09
Reexperiencing	1.1 ± 2.1	4.2 ± 6.2	−3.72	0.001
Hyperarousal	4.4 ± 5.1	7.0 ± 7.6	−1.49	0.14
Avoidance	5.8 ± 3.2	8.3 ± 8.9	−0.47	0.64

Square-root transformation was performed for CAPS total and symptom cluster scores before *t*-tests; CAPS: Clinician Administered PTSD Scale.