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Treatment of Anxiety Prior to a Medical Procedure using an Atenolol - Scopolamine Combination Drug

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Abstract

Objective: Patients often experience anxiety in anticipation of medical procedures. A new class of anti-anxiety medications, PanX®, has been developed as alternatives to benzodiazepines, and is combinations of beta blockers and antimuscarinic motion sickness agents. An atenolol - scopolamine HBr drug combination was tested in an open label physician-sponsored study in patients experiencing anxiety in anticipation of a medical procedure.

Methods: Eight patients were assessed in a pain management clinic. They experienced anxiety prior to an electromyography procedure and consented to a physician-sponsored study using a compounded medication of atenolol - scopolamine HBr delivered by the oral mucosal route. A pair of questionnaires assessed their overall level of anxiety and their individual symptoms of anxiety prior to the anxiolytic treatment and then during the procedure that commenced ca. 10 - 20 minutes after drug administration.

Results: All eight patients remained clear minded and none reported any side effects. Seven of eight patients perceived a calming effect from the drug treatment. Six of eight patients were responders to the treatment and experienced a reduction in anxiety on a 10-point scale from an average of 6.3 points prior to the procedure to 2.7 points during the procedure. Eight individual anxiety symptoms were assessed and all six responders exhibited reductions in the number and/or severity of symptoms.

Conclusion: This open label study provides proof-of-principle of a fast-acting anxiolytic effect upon patients' overall anxiety and individual symptoms due to anticipation of a medical procedure. The atenolol – scopolamine HBr combination was well tolerated without any reported side effects. This medication may be useful in calming the anxiety of patients prior to a variety of medical and dental procedures, and as an alternative to benzodiazepines without using any addictive substances.

Keywords: Beta blocker; Antimuscarinic; Anxiolytic; Medical procedure; PanX®

Introduction

Benzodiazepines (e.g., alprazolam, clonazepam) are the FDA-approved standard-of-care *pro re nata* (PRN) treatments for acute anxiety. Although effective, they pose many problems for patients and prescribing physicians, such as dependence, addiction, abuse, risk of death in combination with opioids, tolerance, and impaired cognition and reaction time [1-4]. The only other FDA-approved products for the short-term treatment of anxiety include buspirone or the antihistamine, hydroxyzine. However, neither of these drugs is generally considered by psychiatrists to be substantially effective at treating acute anxiety episodes. Overall, physicians have a very short list of FDA-approved options for the PRN treatment of anxiety, and each of those options is less than ideal.

Alternatives to benzodiazepines are of particular interest for the management of pain and for multiple significant reasons:

• Patients affected by mood and anxiety disorders are twice as likely to be prescription opioid users [5]. A recent epidemiologic study determined that 18.7 percent of patients with mood and anxiety disorders are users of prescription opioids compared to only 5.0 percent of patients without mood and anxiety disorders [5].

• In 2016 the FDA issued a black box warning against coincident use of opioids and benzodiazepines, due to increased likelihood of death.

• Benzodiazepines are commonly used to treat the symptoms of withdrawal in drug addicts, including those dependent on opioids.

• The USA is experiencing an "Opioid Crisis" with approximately 64,000 overdose fatalities in 2016, of which more than half are due to opioids, such as fentanyl and heroin. This "benzodiazepine - opioid dilemma" poses many challenges to pain management physicians, psychiatrists, and other medical providers, as it limits pharmacologic options for the treatment of moderate-to-severe pain, as well as anxiety disorders. Thus, there is a need for effective, fast-acting, and safer anxiolytic treatments.

Here we present a new approach, a drug combination of a beta blocker and an anti-muscarinic motion sickness agent. PanX® medicines are a patented new class of anxiolytics intended for the "as needed" (PRN) treatment of the symptoms of acute anxiety [6]. Beta blockers affect the sympathetic nervous system by inhibiting the binding of catecholamines (e.g., epinephrine) to beta adrenergic receptors. Beta blockers (e.g., atenolol, propranolol) have been prescribed off-label for decades to suppress the cardiovascular symptoms of acute anxiety, most notably tachycardia and palpitations in performance anxiety [6].

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However, a beta blocker alone does not address the CNS and other non-cardiovascular symptoms of anxiety. Therefore, a muscarinic receptor antagonist, of which scopolamine is one of the most potent, is included in the drug combinations. Scopolamine affects the parasympathetic nervous system's CNS and other symptoms of anxiousness, fear, avoidance, sweating, nausea, and vomiting [6]. The drug combinations were designed to address acute anxiety episodes using well known active ingredients that lack addictive properties.

Physician-sponsored studies of compounded atenolol - scopolamine have recently provided initial evidence of anxiolytic effectiveness in humans affected by anxiety disorders or conditions. A series of case reports were published resulting from studies within a psychiatry setting. A patient with post-traumatic stress disorder (PTSD) experiencing acute anxiety episodes (e.g., breakthrough anxiety manifesting as panic attacks) following psychotherapy sessions was successfully treated PRN by this combination [7]. Two other patients with PTSD also benefited from this particular beta blocker - antimuscarinic combination [8,9]. In addition, a physician-sponsored study in a pain management setting involved three patients with acute anxiety symptoms, who were effectively treated by the drug combination [10]. In aggregate, these articles provided evidence of a rapid-acting anxiolytic benefit with a self-awareness of a calming effect that persisted for hours.

Anticipation of medical procedures can produce varying degrees of anxiety, such as anxiousness, nervousness, and/or fear. In severe cases it might be diagnosed as a specific phobia of the "blood-injection-injury type" [11], with an estimated prevalence of 3.5 percent [12]. The fear of invasive medical procedures is also referred to as tomophobia [11]. There are many examples of clinical procedures and processes that can produce anticipatory anxiety or phobia, including invasive diagnostics, surgeries, biopsies, wound and burn treatments, gynecologic exams, hemorrhoid treatments, laser treatments, tooth extractions, physical therapy, and enclosed radiologic diagnostics (e.g., MRI), among others. Anticipatory anxiety can lead some patients to avoid, delay, or minimize appropriate medical care. Procedure-related anxiety can be addressed pharmacologically, for instance with PRN benzodiazepines, as well as by non-medical alternative approaches [13].

Here we present a proof-of-principle physician-sponsored open label study in the context of anticipatory anxiety associated with a medical procedure, which in this case was electromyography (EMG).

Methods

Eight adult patients were assessed and/or treated in a pain management clinic. Each also mentioned experiencing some level of anxiety in anticipation of a planned EMG procedure. Written informed consent was obtained from all patients to participate in a physician-sponsored study of their anxiety symptoms prior to and following treatment with a commercially-available compounded pharmaceutical, for which the physician anticipated the patients might benefit. The informed consent permitted the use the patients' results in publications, albeit subject to patient confidentiality. None of patients (or clinicians) received any compensation for participation.

Each patient was treated by the oral mucosal route with a prescription compounded drug combination of atenolol 25 mg - scopolamine HBr 0.2 mg in an orally-disintegrating triturate tablet (in mannitol) that was prepared by National Pain Custom Pharmacy (AL).

The patients completed a questionnaire prior to administration of the drug, and then 10 - 20 minutes after drug administration the physician commenced an EMG procedure. Afterwards they completed a second questionnaire on what they recalled of their experience during the procedure. The pair of questionnaires addressed their symptoms and the effects of the medicine. The selected criteria included: overall level of anxiety (anxiety, stress, or nervousness) before and during the procedure (10 point-scale, with 10 as severe); calming effect (y/n); clear mindedness (y/n); side effects (y/n and list); other anti-anxiety medicines (y/n and list); and eight individual symptoms (none, mild, moderate, severe; converted to 0-3 points) included dry mouth, rapid heart rate/heart pounding (tachycardia), unusual sweating, nausea, numbness/tingling, shortness of breath, headache, and trembling/shaking (tremors). This short list of symptoms was selected based upon the symptomology of acute anxiety episodes (most notably panic attack as an exemplar) that we anticipated would likely be affected by the PRN anxiolytic drug combo or might emerge as side effects of this treatment.

Results

The atenolol - scopolamine drug combination was well tolerated in all subjects. Table 1 summarizes the results of the eight patients. All patients reported that they remained clear-minded, i.e., they had no awareness of impairment of cognition. None of the patients reported any side effects of the atenolol - scopolamine HBr medication.

Seven of the eight patients stated that they perceived a "calming effect" from the medication, including one subject (patient J) deemed as a non-responder based upon that patient's anxiety score difference. Treatment resulted in a reduction in anxiety score (10-point scale) during the procedure in six of the eight patients, with an average reduction of 3.6 points in those deemed to be responders (6.3 prior to vs. 2.7 during). Two patients deemed to be non-responders had an average increase of 1.0 point on the anxiety score (5.5 prior to vs. 6.5 during). In aggregate, the overall reduction in the anxiety score was 2.5 points in all eight patients (6.1 prior to vs. 3.6 during). Note that one of the six responders recorded the maximum possible reduction.

Eight individual symptoms were assessed on a 0-3 point scale (none, mild, moderate, severe). All six of the responders stated reductions in the number and/or severity of their symptoms (Table 1). Note that the reductions in anxiety score or in individual symptoms occurred even though the patients were being assessed in the second questionnaire for their recalled experiences during the minimally-invasive EMG procedure that might have produced some (additional) anxiousness at that time, rather than in anticipation of the procedure. In other words, one may speculate that the pain and or fear experienced during the procedure are another variable that might have increased the level of anxiety within some patients (e.g., the two non-responders). Regardless, six of eight were responders on the 10-point anxiety scale and seven of eight declared a perceived calming effect of the medication.

Five of eight patients reported having been prescribed at least one other anxiolytic prophylactic or therapeutic drug. None, some, or all of these five patients might have been under the influence of a prescription anxiolytic drug at the time of the in-office study, although this was not verified by analytical chemistry.

Discussion

The PanX® drugs were developed to provide PRN alternatives to benzodiazepines, without the use of any addictive active ingredients. Atenolol is a beta-1 selective antagonist of adrenalin's binding to adrenergic receptors that have been shown to be beneficial in performance anxiety, alcohol withdrawal, and flight phobia [14-18]. Scopolamine is a high potency muscarinic receptor antagonist

Patients	Anxiety Prior to Procedure	Anxiety During Procedure	Change in Anxiety	Calming Effect	Clear Mind	Symptoms Prior to Procedure	Symptoms During Procedure	Side Effects	Other Prescription Anxiolytic
D	10	1	-9	Yes	Yes	Dry Mouth 1, Tachycardia 1, Short Breath 1, Headache 1	Numbness 1	No	No
E	7	3	-4	Yes	Yes	Dry Mouth 1, Nausea 1, Trembling 1		No	Lorazepam
F	4	1	-3	Yes	Yes	Tachycardia 1, Headache 1, Trembling 1		No	No
G	8	6	-2	Yes	Yes	Dry Mouth 1, Tachycardia 1	Numbness 1	No	Alprazolam
H	7	5	-2	Yes	Yes	Dry Mouth 3, Tachycardia 1, Sweating 2, Nausea 2, Numbness 3, Short Breath 2, Headache 2, Trembling 1	Dry Mouth 3, Tachycardia 2, Sweating 1, Nausea 1, Numbness 2, Short Breath 1, Headache 1	No	Alprazolam
I	2	0	-2	Yes	Yes	Dry Mouth 1, Nausea 1, Numbness 1, Headache 1		No	Duloxetine
J	5	6	1	Yes	Yes	Dry Mouth 1, Tachycardia 1, Sweating 1, Numbness 1	Dry Mouth 2, Tachycardia 1	No	Sertraline
K	6	7	1	No	Yes	Dry Mouth 3, Tachycardia 1, Nausea 1, Short Breath 1, Trembling 2	Dry Mouth 2, Tachycardia 2, Nausea 1, Short Breath 1, Trembling 1	No	No
Ave or %	6.13	3.63	-2.50	87.5%	100%			0%	62.5%

Anxiety on a 10-point scale (10 is severe); Symptoms on a 0 – 3 point scale (0 none, 1 mild, 2 moderate, 3 severe). Patients D, E, F, G, H, and I were responders; Patients J and K were non-responders.

Table 1: Open label study of atenolol – scopolamine HBr in eight patients undergoing an EMG procedure.

that likely affects anxiety/mood symptoms via the M2 and/or M1 receptors of the CNS [19]. Scopolamine was known over a century ago to produce a calming effect in psychiatric patients [20], although this property is not well known today among medical providers. There is clinical evidence that other antimuscarinic agents (e.g., promethazine), can also provide some anxiolytic benefit [6].

Beta blockers and antimuscarinic agents are included in the PanX® combinations not only for pharmacologic targeting of the sympathetic beta-1 and parasympathetic M2/M1 receptors, but also in view of historic safety. Both classes of drugs have been used in millions of patients over five decades and are known to be safe. Neither class is addictive. In addition, the high prevalence of use strongly suggests that both classes of medicines have been coincidentally and/or concurrently used in the same patient(s) as separate prescriptions and/or OTC drugs, for instance a prescription beta blocker for hypertension and a prescription or OTC antimuscarinic agent for motion sickness, nausea, or vomiting. Even with high coincident and/or concurrent use, there is no evidence in the population of producing side effects or drug-drug interactions that extend beyond those inherent within either of the monotherapies.

Prior to this open label study, case series resulting from physician-sponsored studies of compounded atenolol - scopolamine provided initial evidence of effectiveness in the PRN treatment of anxiety. Three patients diagnosed with PTSD, who experienced acute anxiety episodes, were treated effectively by a psychiatrist [7-9]. In addition, three patients with acute anxiety symptoms under the care of pain management physicians were treated successfully [10].

In the present physician-sponsored open label study we document a trial of a compounded combination drug regarding anxiolytic efficacy and with no side effects in eight adult patients. The drug combo produced a fast-acting and beneficial calming effect in 6 of 8 patients, who were deemed as responders. None of the patients described any side effects, and there was no evidence of impairment of cognition.

One can reasonably assert that this beneficial anxiolytic effect might have been enhanced even further under three study design conditions. First, if the inclusion criteria had required each patient to have a high anxiety score prior to the procedure, for instance a minimum of 7 points (with 10 as the maximum), there would have been a greater potential for a difference pre-treatment vs. during the procedure. The six responders had a baseline average of 6.3 points, so there was room for improvement. Of the six responders, two subjects had low baseline anxiety scores (i.e., patient F at 4 points and patient I at 2 points). A higher baseline inclusion parameter could have increased the differential prior to vs. during the EMG procedure.

Second, there might not have been a sufficiently long waiting period between the drug administration and the procedure. One can reasonably assert that if the time interval between dosing and the procedure was increased to a minimum of 30 minutes or more (from the 10 – 20 minutes), the percentage of responders and the magnitude of the response could have been greater. However, it should be noted that often in a clinic time-is-of-the-essence between the patient's initial assessment by the medical provider and the subsequent medical procedure. Some medical providers are willing to pre-treat an anxious patient, typically with an oral benzodiazepine either swallowed intact or pre-dissolved in water, and then have him/her wait (e.g., 30 + min.) for an anxiolytic effect to be acknowledged by the patient. But, some physicians and dentists might be under time constraints or might not be willing to oblige the patient this waiting period. This would not be an obstacle if either the drug has a rapid onset of effect or the patient were to pre-treat themselves immediately prior to arrival at the physician's office, for instance 30-60 minutes in advance. Even under the conditions of this study that the authors consider might have been sub-optimal, this drug combo delivered by the oral mucosal route provided a rapid onset effect as a PRN medication. This anxiolytic benefit may be useful in treating anticipatory anxiety either in-office or prior to arrival.

There is a third limitation to this study to consider. The compounded medicine contained 25 mg of atenolol and 0.2 mg of scopolamine HBr.

For comparison, atenolol is routinely prescribed for hypertension at oral doses of 25 - 100 mg. Scopolamine HBr is routinely prescribed in the US as a transdermal patch for motion sickness, and the device contains 1.5 mg for sustained release over 3 days. Scopolamine HBr is available as an approved over-the-counter drug product for motion sickness in Europe, UK, Australia, and Canada at an oral dose of 0.3 mg [6]. Thus, the selected doses used in the drug combination of this study are considered to be low. It is plausible that higher doses might be more effective, and especially in acute anxiety episodes where time-is-of-the-essence. When considering a higher dose for the combination, possible side effects could impact the upper limits of the selected dosages. For instance, scopolamine doses of 1.2 mg or higher are considered in general to be sedating [6]. High doses of a beta blocker (e.g., 100 mg) might produce bradycardia or hypotension, especially in patients with normal blood pressure. Patients would desire a non-narcotic effect for the PanX® drug combinations, consistent with what was observed in this proof-of-principle study, as well as in the prior case series of physician-sponsored studies.

In 2017, we first reported a rapid-onset beneficial calming effect with atenolol 25 mg - scopolamine HBr 0.2 mg in patients who manifested acute anxiety episodes and were treated PRN. Those patients noted that the perceived beneficial calming effect persisted for multiple hours [7-10]. In the present study design the duration of anxiolytic effect was not assessed, as the patients were not required to remain in-office following the secondary questionnaire.

There is another human clinical report on the coincident use of atenolol and scopolamine [21], albeit unrelated to anxiety disorders or conditions. Twelve healthy male volunteers were subjected to a high heat environment within a sauna in order to assess the effects of elevated temperature upon the cardiovascular system and under the pharmacologic influence of atenolol, scopolamine, or both drugs. The beta adrenergic receptor antagonist effect of atenolol (50 mg) on the cardiovascular symptoms was not abrogated by coincident use of scopolamine (0.3 mg). The antimuscarinic was intended to inhibit sweating in the high heat environment. The authors concluded, *"A small oral dose of Scopolamine alone or in combination with Atenolol produced no marked cardiovascular strain in healthy men during a sauna bath."* This provides additional evidence of the safe concurrent use of atenolol and scopolamine in humans, even under environmental challenge.

Five of the eight patients self-declared that they had received prescriptions for another anti-anxiety medication, although we did not determine if those patients were under the influence of those drugs at the time of the study. This underscores that those five patients were likely under the care of other physicians for an anxiety or a mood disorder. Although two of the six responders had not been prescribed any anxiolytic drug, the other four responders reported prescriptions for lorazepam, alprazolam, or duloxetine. Yet, even though some patients might have been under the influence of a prescription anxiolytic drug at the time, the six individual responders to the combo drug experienced anxiety symptoms (or breakthrough anxiety if already medicated) and perceived qualitative and quantitative symptomatic relief during the medical procedure. We did not require the patients to be anxiolytic drug-naïve to participate, as use of anxiolytic prophylactics (benzodiazepines or SSRIs) is common among pain management patients. But, even patients on prophylactics can encounter heighten anxiety or acute anxiety episodes under certain circumstances. At those times a fast-acting PRN treatment may be beneficial for breakthrough anxiety.

Conclusion

It is common for patients to manifest anxiousness and other symptoms of anxiety disorders in anticipation of undergoing a medical or dental procedure, even in normal patients without anxiety disorders. There are three FDA-approved approaches for short-term or PRN treatment of acute anxiety, i.e., benzodiazepines, buspirone, and hydroxyzine. However, there is a general perception by many healthcare providers and patients that buspirone and hydroxyzine aren't substantially effective. When medical intervention is required in-office a physician typically provides a PRN benzodiazepine, which is often effective. But, benzodiazepines have many detrimental side effects. Therefore, the PanX® drug combinations of a beta blocker with an antimuscarinic agent are a promising new class of fast-acting anxiolytics without using addictive ingredients, and in particular that can be used PRN on occasions of acute anxiety. This open label proof-of-principle study demonstrates for the first time that an atenolol - scopolamine drug combination can be beneficial as an anxiolytic treatment prior to medical procedures.

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References

1. Greenblatt DJ, Shader RI (1978) Dependence, tolerance, and addiction to benzodiazepines: clinical and pharmacokinetic considerations. Drug Metab Rev 8: 13-28.
2. Griffiths RR, Johnson MW (2005) Relative abuse liability of hypnotic drugs: a conceptual framework and algorithm for differentiating among compounds. J Clin Psychiatry 66 Suppl 9: 31-41.
3. Kan CC, Breteler MH, Zitman FG (1997) High prevalence of benzodiazepine dependence in out-patient users, based on the DSM-III-R and ICD-10 criteria. Acta Psychiatr Scand 96: 85-93.
4. Lalive AL, Rudolph U, Lüscher C, Tan KR (2011) Is there a way to curb benzodiazepine addiction? Swiss Med Wkly 141: p. w13277.
5. Davis MA, Lin LA, Liu H, Sites BD (2017) Prescription Opioid Use among Adults with Mental Health Disorders in the United States. J Am Board Fam Med 30: 407-417.
6. Dooley TP (2015) Treating anxiety with either beta blockers or antiemetic antimuscarinic drugs: A review. Mental Health in Family Medicine 11: 89-99.
7. Benjamin A, Mollner A, Dooley TP (2017) Atenolol - scopolamine combination drug decreases acute anxiety post trauma therapy session. Ann Depression and Anxiety 4: 1086.
8. Benjamin AB, Dooley TP (2017) Beta blocker - scopolamine combination drug decreases acute anxiety in a PTSD patient - A Case Report. ARC Journal of Psychiatry 2: 1-4.
9. Benjamin AB, DooleyTP (2017) A compounded, nonbenzodiazepine option for treating acute anxiety. Current Psychiatry 16: e1-2.
10. Thomas T, Benjamin AB, Dooley TP (2017) Treatment of acute anxiety episodes in patients using a fast-acting beta blocker - scopolamine combination drug. Annals of Depression and Anxiety 4: 1088.
11. Schmid M, Robert CW, Roland WF, Schönfeldt-Lecuona C (2009) Tomophobia, the phobic fear caused by an invasive medical procedure - an emerging anxiety disorder: A case report. J Med Case Rep 3: 131.
12. Bienvenu OJ, Eaton WW (1998) The epidemiology of blood-injection-injury phobia. Psychol Med 28: 1129-1136.

13. Landier W, Tse AM (2010) Use of complementary and alternative medical interventions for the management of procedure-related pain, anxiety, and distress in pediatric oncology: An integrative review. J Pediatr Nurs 25: 566-579.

14. Neftel KA, Adler RH, Käppeli L, Rossi M, Dolder M (1982) Stage fright in musicians: A model illustrating the effect of beta blockers. Psychosom Med 44: 461-469.

15. Kraus ML, Gottlieb LD, Horwitz RI, Anscher M (1985) Randomized clinical trial of atenolol in patients with alcohol withdrawal. N Engl J Med 313: 905-909.

16. Horwitz RI, Gottlieb LD, Kraus ML (1989) The efficacy of atenolol in the outpatient management of the alcohol withdrawal syndrome. Results of a randomized clinical trial. Arch Intern Med 149: 1089-1093.

17. Gottlieb LD, Horwitz RI, Kraus ML, Segal SR, Viscoli CM (1994) Randomized controlled trial in alcohol relapse prevention: Role of atenolol, alcohol craving, and treatment adherence. J Subst Abuse Treat 11: 253-258.

18. Ekeberg O, Kjeldsen SE, Greenwood DT, Enger E (1990) Effects of selective beta-adrenoceptor blockade on anxiety associated with flight phobia. J Psychopharmacol 4: 35-41.

19. Witkin JM, Overshiner C, Li X, Catlow JT, Wishart GN (2014) M1 and m2 muscarinic receptor subtypes regulate antidepressant-like effects of the rapidly acting antidepressant scopolamine. J Pharmacol Exp Ther 351: 448-456.

20. Houde A (1906) Scopolamine: A physiological and clinical study. The American Journal of Clinical Medicine 13: 365-367.

21. Kukkonen-Harjula K, Oja P, Vuori I, Pasanen M, Lange K, et al. (1994) Cardiovascular effects of Atenolol, scopolamine and their combination on healthy men in Finnish sauna baths. Eur J Appl Physiol Occup Physiol 69: 10-15.