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Supra-Additive Toxic Interaction of Nicotine With Antihistamines, and Enhancement by the Proconvulsant Pentylenetetrazole

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SEWELL, R. G., K. P. NANRY, J. KENNEDY, T. R. STIGER AND R. E. HARMON. *Supra-additive toxic interaction of nicotine with antihistamines, and enhancement by the proconvulsant pentylenetetrazole.* PHARMACOL BIOCHEM BEHAV 22(3) 469–477, 1985.—Antihistamines are being increasingly administered in combination with various other agents, with adverse drug reactions the frequent result. The present study consisted of two experiments. Experiment 1 examined the toxicological response of rats to nicotine tartrate (0.0, 2.0, 4.0, and 8.0 mg/kg) in combination with either of two H_1-histamine receptor antagonists, the ethylene diamine tripelennamine HCl (0.0, 16.0, 32.0, and 64.0 mg/kg) or the aminoethyl ether diphenhydramine HCl (0.0, 32.0, 64.0, and 96.0 mg/kg). Adult female rats received intraperitoneal injections when housed 12 per cage and toxicological response (number dead per group) was assessed 24 hours post-treatment. The results showed that over the dose ranges employed, and when given alone, nicotine was completely non-lethal, tripelennamine was virtually non-lethal and diphenhydramine was toxic only at the highest dose (5 of 12, at 96.0 mg/kg). However, when nicotine and the antihistamines were delivered in combinations, the toxicological response was markedly altered. Tripelennamine in combination with nicotine yielded supra-additive interaction, with the degree of potentiation being a simple linear function of nicotine within each dose of tripelennamine. The interaction between nicotine and diphenhydramine was more complicated, with certain dose combinations yielding supra-additivity, yet with others yielding antagonism. It was suggested that seizure-precipitated cardiopulmonary collapse was the immediate cause of death, plausibly mediated by central mechanisms. As such, Experiment 2 examined the influence of adding the proconvulsant pentylenetetrazole (PTZ) (0.0, 10.0, and 20.0 mg/kg) to nicotine (0.0, 2.0, 4.0, and 8.0 mg/kg)-tripelennamine (0.0 and 32.0 mg/kg) combination treatments. Effects were assessed both at 1.0 and 24.0 hours post-injection. Results showed that PTZ dramatically enhanced the degree of nicotine-tripelennamine toxic interaction, at doses where each of the three drugs was totally non-lethal when given alone. In addition, clonic-tonic convulsions were commonly noted. The results collectively supported the notion that centrally mediated seizure might indeed be related to the immediate cause of death. Results are discussed in terms of other assays with which such interactions might be observed, particularly those procedures employing behavioral endpoints and lower, non-toxicological doses.

Nicotine Tripelennamine Diphenhydramine Lethality H_1-histamine receptor antagonists
Pentylenetetrazole Rats Seizure Supra-additivity Adverse drug interactions Drug toxicity

TRIPELENNAMINE is an H_1-histamine receptor antagonist (antihistamine) which is both frequently prescribed for anaphylaxis and allergic reaction (e.g., [32]), and additionally, appears in numerous over-the-counter preparations (e.g., [32]). Effective and safe as prescribed, it has, however, been associated with various cases of intoxication and lethal poisoning (e.g., [74,104]). In addition, due to the rising trend of polypharmacy in medical therapeutics, self-medication and recreational drug abuse (e.g., [11]), tripelennamine has frequently been one component of combination-drug treatments. Recently, interest in drug combinations involving tripelennamine has increased with the emergence of epidemic "recreational" use of tripelennamine administered with the mixed agonist-antagonist narcotic pentacozine (e.g., [11, 22, 26, 56, 71, 83, 99]). Self-administration of this narcotic-antihistamine (so-called "T's and Blu's") combination, while offering various euphoric effects, presents certain formidable risks for the drug abuser (e.g., [55]) including major motor seizures, psychiatric complications, and lethality (e.g., [69]). Laboratory investigations have corroborated clinically observed toxic synergism existing between pentazocine and tripelennamine (e.g., [101]), and have further shown that this interaction can be considerably modulated by the current environment (e.g.,

[72]). Tripelennamine has been reported to adversely interact with various other central nervous system (CNS) depressants (e.g., [44]. In an effort to explore which other drugs may toxicologically interact with tripelennamine, we began adding nicotine tartrate treatments to narcotic-antihistaminic challenges with rodents, reasoning that street drug abusers frequently and simultaneously self-administer nicotine. We soon noted that which appeared to be marked supra-additive interactions between tripelennamine and nicotine, per se.

Tripelennamine was one of the first H_1-histamine receptor antagonists synthesized [107]. It is a member of the ethylene diamine class, which is recognized to produce more "CNS stimulation" than the other classes of H_1-antagonists. In total, there are five other classes of H_1-receptor antagonists including amino ethyl ethers, propylamines, piperazines, piperidines, and the phenothiazines [63], and it has remained unclear whether suspected supra-additive interactions with nicotine were unique to the ethylene diamines or whether this reaction was common to other H_1-receptor antagonists. We therefore decided to examine the generality of this reaction amongst H_1-antagonists by choosing an agent, diphenhydramine, from a second H_1-antagonist class, the amino ethyl ethers. Shannon and Su [82] have found, for instance, that while concurrent administration of tripelennamine with pentazocine enhanced morphine-like discriminative stimulus effects of pentazocine in a rat drug-discrimination procedure, diphenhydramine did not. Such results suggest that H_1-antagonists may interact very differently with other psychoactive agents depending upon their respective chemical class. The purpose of Experiment 1, then, was twofold: (1) to analyze whether tripelennamine interacts with nicotine to determine toxicological response in rats, and (2) to establish whether diphenhydramine interacts with nicotine in a similar manner.

EXPERIMENT 1

METHOD

Subjects

Three hundred and thirty-six female rats of the Sprague-Dawley strain, born and reared in our colony, served as subjects. Subjects were raised in groups of six same-sex conspecifics per cage, and tested in adulthood at an average weight of 279±2 g (mean±S.E.). Before and during the experiment, subjects were given unlimited access to Purina Laboratory Rodent Chow (Ralston-Purina Co., St. Louis, MO) and water in a constantly illuminated colony maintained at 24–26°C.

Apparatus, Procedure and Drug Preparation

The lethality of nicotine tartrate (ICN Pharmaceutical, Inc., Plainview, NY) at doses of 0.0, 2.0, 4.0, and 8.0 mg/kg was examined alone and in combination with either 16.0, 32.0 and 64.0 mg/kg tripelennamine hydrochloride (Sigma Chemical Co., St. Louis, MO) or with 32.0, 64.0 and 96.0 mg/kg diphenhydramine hydrochloride (Sigma Chemical Co., St. Louis, MO). Thus, all dose levels of nicotine were tested in combination with all dose levels of tripelennamine, and of diphenhydramine; this design additionally allowing for assessment of nicotine, tripelennamine and diphenhydramine toxicities when each agent was given alone. The aforementioned dose ranges, stated as the salts, were selected by reference to previous studies of these drugs, given alone, to rodent subjects (e.g., for nicotine: [12, 88, 89]; for tripelennamine: [33, 67, 95]; for diphenhydramine: [39, 40, 106]). A total of 28 drug treatment groups was thus generated, with each composed of 12 randomly selected subjects. No subject received more than one treatment condition. Nicotine, tripelennamine, and diphenhydramine were each separately dissolved into physiological saline and delivered intraperitoneally (IP) at volumes of 1.0 ml/kg. Thus, each animal received two, virtually simultaneous IP injections of either (1) saline plus one of the three test compounds, or (2) saline plus saline, or (3) nicotine plus tripelennamine, or (4) nicotine plus diphenhydramine. Lethality per group was assessed 24 hours post-injection.

Statistical Analysis

Within each constant dose of tripelennamine, and within each constant dose of diphenhydramine, Chi-square tests were used to test mortality differences at the varying nicotine doses. For situations in which substantial mortality existed, a test for linearity, as described by Fleiss [37], was employed. Basically this method involves relating the proportion dead to the dose of nicotine by a fitted straight line. This model is then tested by Chi-square for goodness-of-fit. All decisions of statistical significance were based on $p<0.05$.

RESULTS

No animal which received saline-saline control injections died, as was expected. No dose of nicotine, given alone, produced any lethal toxicity (these data are therefore not represented graphically). The top three graphs of Fig. 1 display those data collected from tripelennamine challenges in combination with various nicotine doses. Inspection of Fig. 1 shows that no dose of tripelennamine, given alone, produced lethal reaction, save the 64.0 mg/kg dose level wherein one subject died. However, when tripelennamine (16.0, 32.0 and 64.0 mg/kg) was given in combination with various doses of nicotine (2.0, 4.0, and 8.0 mg/kg), marked and dose-related lethal toxicities resulted. In general, as dose of nicotine increased within any given tripelennamine dose, so too did the probability of death. Further, at a given nicotine dose, as tripelennamine dose was increased, the probability of lethal reaction rose. Thus, for example, at the 8.0 mg/kg nicotine level tripelennamine at 16.0 mg/kg produced one death, tripelennamine at 32.0 mg/kg produced two deaths, while the 64.0 mg/kg yielded 12. The effect of nicotine dose upon toxicity within a given tripelennamine dose was significant for the 64.0 mg/kg dose group (Chi-square=20.476, $df=3$, $p<0.0001$), but not at the 16.0 or 32.0 mg/kg levels. The test for linearity for the 64.0 mg/kg dose group revealed that a linear model indeed fit the data well. Collectively, these data demonstrated a supra-additive toxic interaction between nicotine and tripelennamine. A clear example of this supra-additivity can be seen for the 8.0 mg/kg nicotine-64.0 mg/kg tripelennamine combination where the nicotine challenge given alone yielded 0 deaths and the tripelennamine given alone produced only one, yet given in combination, these two agents produced 12 deaths.

The data relating the effects of all diphenhydramine challenges are presented in the bottom three graphs of Fig. 1. Here it can be seen that diphenhydramine-alone produced lethal reaction only at the highest dose level (96.0 mg/kg) wherein five deaths occurred. Diphenhydramine at 32.0

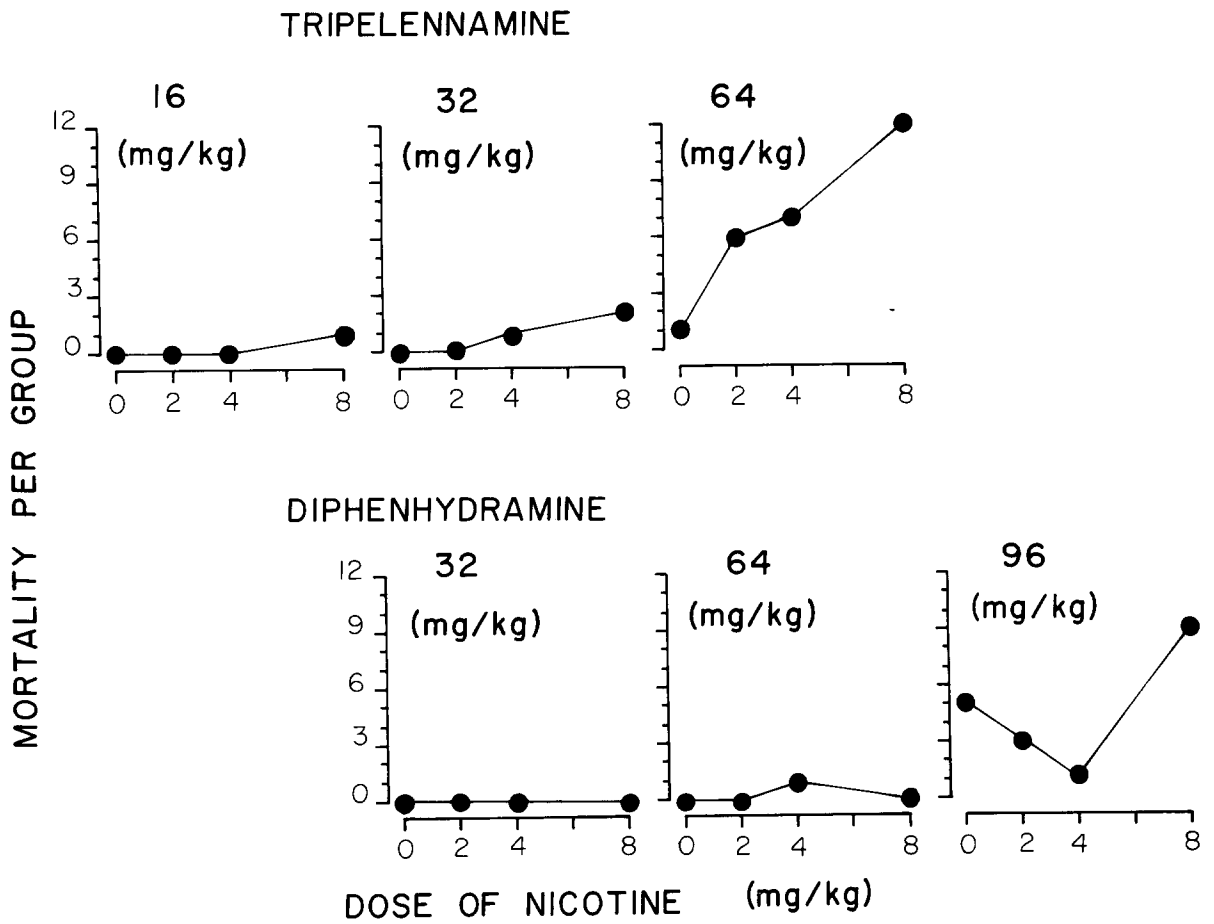

FIG. 1. The effects of tripelennamine and of diphenhydramine, each when given alone and in combination with varying doses of nicotine, upon mortality experienced by group-housed rats (N=12/group) as assessed 24 hours post-injection.

mg/kg produced no lethalities, regardless of the nicotine combination dose. Diphenhydramine at 64.0 mg/kg also produced no lethal reactions, regardless of nicotine combination dose, save a single death at the 4.0 mg/kg nicotine level. A very different picture emerged for the 96.0 mg/kg diphenhydramine groups. Here, the lower nicotine doses (2.0 and 4.0 mg/kg) actually suppressed lethality vis à vis diphenhydramine given alone, and thus yielded a subtractive interaction. For the highest nicotine level (8.0 mg/kg), in combination with 96.0 mg/kg diphenhydramine, there occurred nine deaths and thus a clear elevation as compared to diphenhydramine alone. Only with the 8.0 mg/kg nicotine-96.0 mg/kg diphenhydramine group could a supra-additive interaction be ascertained to have occurred. Chi-square analysis of data collected under the 96.0 mg/kg diphenhydramine challenge showed mortality to differ significantly as a function of nicotine dose ($p<0.006$). However, the test for linearity indicated large departures from linearity and that the relationship was much more complex than a simple, straight-line function.

EXPERIMENT 2

In Experiment 1 a supra-additive toxic interaction was found for nicotine given in combination with either of the H_1-histamine receptor antagonists, tripelennamine or diphenhydramine. This synergism could have accrued via any of several different mechanisms. Visual inspection of subjects during study revealed severe tonic-clonic convulsive activity and very labored breathing preceding death. It was hypothesized, therefore, that convulsive seizures may have been causally linked in the present lethal toxicities. Various evidence, taken from the pharmacology of nicotine and each of the two antihistaminic agents supports this view.

The purpose of Experiment 2 was to analyze further the possibility that convulsive seizures were causally related to the observed toxic synergism between nicotine and tripelennamine. Tripelennamine (0.0 vs. 32.0 mg/kg) was selected for further analysis, over diphenhydramine, since Experiment 1 had shown the interaction between it and nicotine to be a good deal more straightforward than that for diphenhydramine. The technique selected was to independently manipulate degree of seizure susceptibility of subjects receiving various nicotine-tripelennamine combinations. This was done by simultaneously treating subjects with one of three sub-lethal, sub-convulsive doses (0.0, 10.0, or 20.0 mg/kg) of the established pro-convulsant, pentylenetetrazole. Much research has shown that pentylenetetrazole (PTZ) does predispose mammals to seizure susceptibility, that these effects are dose-related, that PTZ exerts its seizure-induction effect by acting on CNS mechanisms directly, and that PTZ treatment is a useful laboratory model with which to analyze

epileptic seizure processes (e.g., [14, 21, 60, 68, 81, 90]). Further, various investigators have employed PTZ to examine the extent to which other drugs may modify seizure threshold (e.g., [20, 30, 46, 49, 73, 91]). If PTZ were to enhance lethality rates, and simultaneously observed severity of seizure in nicotine-antihistamine treated subjects, this would lend further credence to the notion that CNS-mediated seizure processes were causal in nicotine-antihistamine toxic synergism.

METHOD

Subjects

Two hundred and eighty-eight female rats of the Sprague-Dawley strain, born and reared in our colony, served as subjects. Subjects were raised in caged groups of six same-sex conspecifics, and tested in adulthood at an average weight of 310±2 g (mean±S.E.). The colony was illuminated on a twelve hour day:night cycle. Subjects were alike in all other respects to those subjects of Experiment 1.

Apparatus, Procedure and Drug Preparation

The apparatus and procedure of Experiment 2 were essentially the same as those employed in Experiment 1, with minor exceptions. The lethality of nicotine tartrate at doses of 0.0, 2.0, 4.0, and 8.0 mg/kg was examined alone and in combination with 0.0 or 32.0 mg/kg tripelennamine hydrochloride, and with 0.0, 10.0, or 20.0 mg/kg of the proconvulsant pentylenetetrazole (Sigma Chemical Co., St. Louis, MO). A total of 24 drug treatment groups was thus constituted, with each composed of 12 randomly selected subjects. The doses of tripelennamine and nicotine were selected on the basis of results from Experiment 1, while sub-convulsive, sub-lethal doses of pentylenetetrazole were selected by reference to published literature (e.g., [90]). As in Experiment 1, all drug treatments were prepared by dissolution into physiological saline and administered IP at volumes of 1.0 ml/kg. Each animal received three, virtually simultaneous injections of ((a) nicotine, (b) tripelennamine, and (c) pentylenetetrazole), with the only exception being that those animals which received nicotine alone, also received only a single saline control injection, rather than two saline control injections. This exception being because Experiment 1 showed that nicotine-only treatments, given with saline-control injections, were totally non-lethal. Rather than undergo needless duplication to re-establish this point, with an additional saline-control injection, those nicotine-plus-saline control animals of Experiment 1 were simply reconsidered in the analysis of Experiment 2. This is to be contrasted with the tripelennamine or the pentylenetetrazole-alone groups wherein each animal received two additional injections of saline vehicle control. Lethality was assessed both at 1.0 hours after injection and then again at 24.0 hours after injection to ascertain whether toxicological response further accrued over this period.

Statistical Analysis

Contingency tables were formed and Chi-square tests then used to test mortality differences for all animals receiving tripelennamine at 32.0 mg/kg. Briefly, within each constant dose of nicotine the influence of varying PTZ dose was assessed, and similarly, within each constant dose of PTZ the influence of varying nicotine dose was examined.

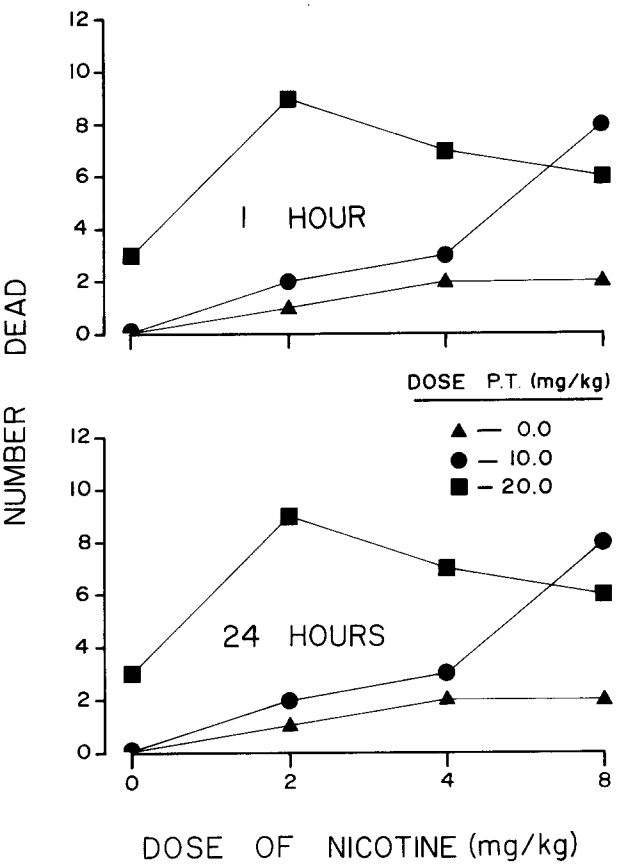

FIG. 2. The effects of the proconvulsant pentylenetetrazole and nicotine, each at several doses in combination with tripelennamine at 32.0 mg/kg, upon mortality experienced by group-housed rats (N=12/group) assessed both at 1.0 and 24.0 hours post-injection.

RESULTS

When tripelennamine was not presented (i.e., 0.0 mg/kg), no animal died, regardless of nicotine, pentylenetetrazole, or nicotine-pentylene-tetrazole combination treatment (these data are therefore not represented graphically). Figure 2 displays those data collected under tripelennamine challenge at 32.0 mg/kg in combination with pentylenetetrazole at 0.0, 10.0 and 20.0 mg/kg and nicotine at 0.0, 2.0, 4.0 and 8.0 mg/kg, wherein the top panel is for data collected at 1.0 hr post-injection while the bottom panel is for data at 24.0 hr post-treatment. As shown, tripelennamine was totally non-lethal when given alone at 32.0 mg/kg; this result corroborating that of Experiment 1. However, combination administration of various non-lethal doses of nicotine, PTZ and tripelennamine doses together, did yield considerable lethality. This constitutes a "supra-additive" or "synergistic" set of interactions. Under tripelennamine at 32.0 mg/kg, the following set of results emerged, which were not observed when tripelennamine was absent: (1) addition of nicotine under PTZ at 0.0 mg/kg (signified by triangles) produced lethality at 2.0, 4.0 and 8.0 mg/kg (a significant effect of nicotine dose being absent however, $p<0.483$), (2) addition of nicotine under PTZ at 10.0 mg/kg (signified by circles) produced enhanced lethality at 2.0, 4.0 and 8.0 mg/kg over that which was obtained at PTZ=0.0 mg/kg (effect of nicotine dose being significant, $p<0.002$); (3) addition of

nicotine under PTZ at 20.0 mg/kg (signified by squares) also produced dramatically enhanced lethality at 2.0, 4.0 and 8.0 mg/kg over that obtained at PTZ=0.0 mg/kg (effect of nicotine dose approached, but did not reach, statistical significance, $p<0.100$). When results were analyzed for influence of PTZ dose under tripelennamine at 32.0 mg/kg, significance was found dependent on nicotine dose level. Thus, influence of PTZ dose was significant when nicotine equalled 0.0 mg/kg ($p<0.038$), 2.0 mg/kg ($p<0.001$) and 8.0 mg/kg ($p<0.042$). Incidental visual observation of subjects revealed that (a) little seizure activity occurred under treatment with nicotine or tripelennamine alone; that (b) when PTZ was given alone, little overt convulsion was noted; yet that (c) when PTZ was given with nicotine-tripelennamine combinations, considerable convulsive activity was observed.

In summary, when tripelennamine, nicotine and pentylenetetrazole were examined in isolation, no lethal effects were observed. An interaction between tripelennamine and nicotine existed, as was demonstrated in Experiment 1, and in Experiment 2 was found to be potentiated dramatically by addition of the proconvulsant PTZ. In the presence of tripelennamine (i.e., at 32.0 mg/kg) toxicity was a function of both nicotine and PTZ dose levels. Under the present conditions, tripelennamine's administration was required for PTZ to enhance nicotine's toxicity. As can be noted by comparing top and bottom panels of Fig. 2, no differences existed between lethality observed at 1.0 hours and 24.0 hours, demonstrating that the time-course of these interactions is to be gauged in minutes, not hours. Finally, PTZ enhanced the frequency and severity of incidentally noted clonic seizure activity in subjects receiving nicotine-tripelennamine combinations.

GENERAL DISCUSSION

Experiment 1 demonstrated supra-additive toxic interaction of nicotine with two histamine H_1-receptor antagonists in rats. Results clearly showed potentiation of tripelennamine toxicity by nicotine, and that this effect depended upon both tripelennamine and nicotine dose levels. This result extends previous findings (e.g., [72,101]) by demonstrating that an agent (nicotine) chemically quite distinct from the narcotics can also yield supra-additive toxic interaction with tripelennamine. Potentiation of toxicity was also found for diphenhydramine under nicotine challenge, although diphenhydramine was less potent than tripelennamine in this regard. In addition, certain doses of nicotine were actually demonstrated to antagonize diphenhydramine's toxic action yet the mechanism of this antagonism, and how it pharmacologically differs from that of tripelennamine, remains unknown. Therefore, while supra-additivity was found for both H_1-antagonists analyzed in combination with nicotine, the relation for the ethylene diamine appeared much less complicated than that for the ethanol amine. A review of the literature suggests the present study as the first to report supra-additive interaction of nicotine with any histamine H_1-receptor antagonist in a toxicological, or any other, assay system. It remains to be established as to whether nicotine similarly interacts with any of the other four classes of H_1-receptor antagonists, namely propylamines, piperazines, piperidines, and the phenothiazines, as well as with H_2-receptor antagonists such as cimetidine.

The immediate cause of death resulting from nicotine-antihistamine combination treatment has remained unknown. Clinical descriptions of acute poisoning under nicotine and antihistamines given alone, indicate marked seizure activity preceding general cardiopulmonary collapse. Visual inspection of subjects during Experiment 1 revealed tonic-clonic convulsive activity and labored breathing preceding death. It was therefore hypothesized that convulsive seizure may have been causal in the observed lethalities. Experiment 2 was conducted to explore this possibility. Specifically, the known proconvulsant pentylenetetrazole was administered at three sub-lethal, sub-convulsant dose levels to establish the extent to which nicotine-tripelennamine treatments predispose subjects to seizure, and ensuing death. Pentylenetetrazole is known to act directly on CNS mechanisms to yield electrographic and behavioral seizure (e.g., [14, 21, 60, 68, 81, 90]), and has been used to ascertain the extent to which various chemical and physiological insults change seizure threshold (e.g., [20, 30, 46, 49, 73, 91]). Experiment 2 demonstrated that subconvulsive doses of PTZ dramatically enhanced mortality rates of nicotine-tripelennamine treated subjects. This enhancement was dependent upon both the dose of nicotine and PTZ. In addition, tripelennamine's presence was required in that PTZ remained non-lethal both alone and in all combinations with nicotine only. Casual observation clearly suggested enhanced overt, generalized tonic-clonic seizure for PTZ-treated, nicotine-tripelennamine recipients. Time-course data indicated a rapidity and brevity of effect of less than 1.0 hour. Collectively, these data suggest that seizure thresholds are markedly reduced for nicotine-tripelennamine recipients, that CNS mechanisms may be involved, and that this increased susceptibility to a seizure-inducing agent is related to probability of death. Various evidence, taken from the pharmacology of nicotine and each of the two antihistaminic agents supports these conclusions.

First, tripelennamine has been clearly associated with seizure activity in various populations and laboratory preparations. Convulsive seizures are reported as a frequent and serious complication of tripelennamine-pentazocine self-administration in street users (e.g., [22, 26, 55, 56, 71, 83, 84, 99]). It is well-known among "T's and Blu's" users that antihistamines alone can produce convulsions (e.g., [71]). It has been hypothesized that seizure incidence after self-administration of tripelennamine-pentazocine combinations is probably due to the tripelennamine (e.g., [71]). Various rodent assays of potentiation of lethality by combining tripelennamine with pentazocine have revealed marked seizure activity at times soon after administration [72,101]. Further, tripelennamine enhances convulsive behavior when given alone to morphine-dependent rats [103]. In certain laboratory animal preparations, high-dose treatment with tripelennamine alone has been seen to induce tonic-clonic seizures and CNS "excitation" (e.g., [35,104]). The primary actions of tripelennamine are atropine-like, and it may be that anticholinergic influences contribute to tripelennamine's convulsant action (e.g., [55]). Other authors have speculated that tripelennamine yields convulsions by altering cellular sodium/calcium compositions and membrane permeabilities (e.g., [71]). Neurochemically, tripelennamine is said to exert a cocaine-like action on sympathetic neurons in that it blocks the reuptake of catecholamines and other transmitters (e.g., [50,52]).

Second, diphenhydramine has been associated with numerous CNS-mediated adverse drug reactions (ADR's), including seizures. Diphenhydramine, considered relatively safe, has been implicated, however, in various cases of lethal overdose (e.g., [8, 15, 74]). In addition, the Federal Drug

Enforcement Administration (USA) has stated that the agent has consistently ranked in the Top 50 list of compounds referred to in hospital emergency rooms by drug overdose patients; most recently moving to 27th, above methadone, lysergic acid diethylamide (LSD), and barbituates [27]. Both electroencephalographic (EEG) and behavioral data suggest CNS tissues as important sites of diphenhydramine action. EEG studies of diphenhydramine-treated cats have found epileptiform paroxysms and hypersynchrony at high doses (e.g., [35]). At lower doses, in EEG studies of human volunteers, diphenhydramine has induced EEG patterns characteristic of somnolence [36, 42, 54].

Third, various lines of evidence indicate that nicotine acts directly on CNS to yield numerous influences, including behavioral changes (e.g., [5, 28, 45, 66, 70, 92, 105]). Electrophysiological data collected from the CNS of humans (e.g., [7]), other mammals (e.g., [18,48]), and avians (e.g., [58]) show clear nicotine effects. In addition, convulsive seizures have been found routinely after high-dose nicotine administration (e.g., [1, 2, 3, 85, 87, 94, 106]). Further cardiovascular function rapidly changes under nicotine (e.g., [17, 59, 65, 102]). Such cardiovascular effects appear to be mediated by several disparate mechanisms, notable among these are activational influences on the sympathoadrenal system (e.g., [25, 47, 57]). In addition, Taylor [93] has stated death following nicotine overdose is due to the failure of respiration resulting from both central paralysis and peripheral blockade of muscles of respiration. It therefore appears likely that nicotine-induced lethality is due at least in part to cardiopulmonary changes, mediated by CNS alterations.

There exist two categories of mechanism by which drug-drug interaction occurs (e.g., [4, 43, 61, 96]). Mechanisms of the first type alter concentrations of one or both drugs, at the site of action. Generally, these mechanisms are of four classes: absorption, distribution, biotransformation (metabolism) and excretion (i.e., the A.D.M.E. factors). Mechanisms of the second type involve "classic" pharmacological interaction, whereby "effective concentrations" of agents are altered via mutual presence of two or more drugs. Here, drug effects are modified after molecules actually reach sites of action (or, receptor sites). At present, there is little published evidence to indicate which mechanisms category is involved in the reported effects. It is recognized that multiple types of interaction can occur with the same pair of compounds, and it remains possible that nicotine and H_1-antagonists interact via both A.D.M.E. and classic mechanisms.

An important extrapolation from the present work is that antihistamines may, at much lower doses, interact with nicotine to influence various other biological assays, such as gross-motor behavioral endpoints. Such influence seems at least plausible since studies have shown that each of the three test agents individually possesses considerable activity in assorted behavioral procedures. With rats, tripelennamine has been found to influence water intake, wheel running not preceded by shock, and indices of nocioception [67]. In humans, diphenhydramine has been demonstrated to alter affect, vigilance, sociability, and gross motor movement (e.g., [36,51]). In mice, diphenhydramine has been found to influence exploratory motor activity, grooming behavior, shock-induced attack, the writhing response, salivation, and the righting reflex (e.g., [53]). Nicotine exerts numerous behavioral influences, and these effects appear centrally mediated. The motor activity of rats, for instance, has been observed to change under nicotine (e.g., [9, 19, 24, 48]), as have nocioception (e.g., [78,97], aggression (e.g., [23, 34, 75 100]), water balance (e.g., [10, 79, 98]), and emesis (e.g., [6, 16]). Nicotine has altered numerous operant behaviors (e.g., [12, 29, 38, 64]), effectively reinforced behavior in several species (e.g., [13, 31, 41, 86]), and has functioned as a discriminative stimulus (e.g., [62, 76, 77, 80]). Therefore, in view of the multiple behavioral effects of nicotine and of tripelennamine and diphenhydramine, it appears possible that these may interact, at clinical doses, in various behavioral assays.

In conclusion, a here-to-fore unreported supra-additive toxic interaction has been observed between nicotine and each of two histamine H_1-receptor antagonists, an ethylene diamine and an ethanol amine. The mechanisms by which these toxic interactions occur remain to be identified, but Experiment 2, employing concomitant proconvulsant challenges, suggests seizure activity as related to mechanism of death. The literature and our observations suggest that the immediate cause of death may have been seizure-precipitated cardiopulmonary collapse. In conjunction with relevant behavioral literatures, these results suggest that clinically observable nicotine-antihistaminic interactions may occur, at the behavioral level, in lower dose ranges.

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