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Anticholinesterase (DFP) toxicity antagonism by chronic donepezil: A potential nerve agent treatment

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Abstract

Animal studies exploring the antagonism of irreversible cholinesterase inhibitors (i.e. nerve agents) such as soman and sarin have shown that pretreatment with the reversible centrally acting cholinesterase inhibitor, physostigmine, alone or in conjunction with the centrally acting anticholinergic drug, scopolamine, antagonizes the lethality and toxicity of these agents. This study evaluated the effects of pretreatment with the oral cholinesterase inhibitor and anti-Alzheimer's agent, donepezil (Aricept) on the hypokinetic, hypothermic and diarrhea-inducing effects of the irreversible long-acting cholinesterase inhibitor, diisopropylfluorophosphate (DFP) in adult Sprague–Dawley rats. Donepezil (2 mg/kg), given acutely (30 min pretreatment) or chronically (10 daily treatments), significantly antagonized the hypothermia, hypoactivity and diarrhea induced by DFP (1.25 mg/kg) administration. The effects were most prominent 4 and 6 h after the injection of DFP and some protection was observed even when the last treatment of the chronic donepezil protocol was given 24 h before the DFP injection. Although these phenomena are not the same as lethality, they may be parallel phenomena, and our results may have therapeutic implications for the treatment of nerve agent toxicity.

Keywords: Diisopropylfluorophosphate (DFP); Donepezil; Acetylcholine; Soman; Sarin; Cholinesterase inhibitors; Hypothermia; Diarrhea

1. Introduction

Organophosphorus cholinesterase inhibitors (i.e. diisopropyl fluorophosphate [DFP], sarin, soman, VX) induce toxicity by inhibiting acetylcholinesterase (AChE), the primary enzyme which metabolizes acetylcholine (ACh) in the central nervous system and in smooth and skeletal muscle. Increases in ACh lead to enhanced central and peripheral muscarinic and nicotinic receptor stimulation, with subsequent effects on NMDA and perturbations of other neuroactive chemicals (Taylor, 1996). Cholinergic toxicity consists of lethargy, lassitude, salivation, vomiting, weakness, nausea, bronchoconstriction, muscle paralysis, respiratory paralysis, diarrhea, hypotension, hypertension, bradycardia and death (Taylor, 1996; Heath, 1961).

Pharmacological treatment of AChE inhibitor toxicity conventionally consists of administration of the anticholinergic (i.e. antimuscarinic) agent, atropine sulfate, and the administration of cholinesterase reactivators such as pralidoxime (Taylor, 1996; Heath, 1961; Volans, 1996). However, several preclinical studies indicate that central mechanisms are involved in AChE inhibitor-induced toxicity and mortality. Centrally acting anticholinergic agents such as scopolamine, benztropine, trihexyphenidyl, and aprophen have been shown to be more effective than less centrally acting atropine or methscopolamine in preventing AChE inhibitor-induced toxic effects (Anderson et al., 1994; Janowsky, 2002; Janowsky et al., 1985, 1986, 1987; Lallement et al., 2001; Leadbeater et al., 1985). Also, one study in man indicates that scopolamine is more effective

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than atropine and the non-centrally acting anticholinergic agent methscopolamine in preventing centrally mediated cardiovascular, neuroendocrine and behavioral effects of the reversible cholinesterase inhibitor, physostigmine (Janowsky et al., 1986).

Another strategy used to treat AChE inhibitor toxicity, such as occurs with nerve agents, has been to pretreat with relatively low, non-lethal doses of reversible cholinesterase inhibitors. These agents transiently bind to the AChE molecule and block subsequent binding of long lasting, irreversible AChE inhibitors such as soman, sarin and VX. Previously, enthusiasm existed for prophylactic pretreatment with pyridostigmine, a reversible, peripherally acting oral AChE inhibitor. Pyridostigmine was considered to have some protective effects against organophosphate nerve agents (Dirnhuber et al., 1979; French et al., 1979; Walday et al., 1993; Xia et al., 1981). Because of this, many participants in the Persian Gulf War were given pyridostigmine (Keeler et al., 1991). However, pyridostigmine does not appear to effectively antagonize AChE inhibitor toxicity (Leadbeater et al., 1985; Miller et al., 1993), and indeed, there is some evidence that the toxic effects of irreversible AChE inhibitors are potentiated by pretreatment with pyridostigmine (Overstreet et al., 1998a,b; Lallement et al., 2001).

Pretreatment with subchronic administration of the reversible, short acting centrally active AChE inhibitor physostigmine in guinea pigs and other rodents has proved promising (Anderson et al., 1991; Harris et al., 1991; Lim et al., 1988, 1991; Meshulam et al., 1995; Miller et al., 1993). This is true especially when this pretreatment is given with a centrally acting antimuscarinic receptor blocking agent such as trihexyphenidyl or scopolamine (Lim et al., 1988; Meshulam et al., 1995; Philippens et al., 2000). Thus, pretreatment with physostigmine plus scopolamine or physostigmine plus trihexyphenidyl (Artane) led to complete survival, devoid of convulsions or loss of consciousness in non-human primates in whom soman doses would otherwise have been lethal (von Bredow et al., 1991). Furthermore, centrally active physostigmine was found more effective than non-centrally acting pyridostigmine in protecting against soman and sarin effects (Leadbeater et al., 1985; Miller et al., 1993) and other organophosphate effects as well (Deshponde et al., 1986; Solana et al., 1990).

Even though centrally active physostigmine appears to be an effective pretreatment for AChE inhibitor toxicity in animals, there are several drawbacks to its use. Physostigmine has a short half-life. If it is to be given as a treatment for Alzheimer's disease instead of a prophylactic for nerve agent toxicity, it must be given frequently and in relatively high oral doses (or transdermally or as an ongoing infusion) to maintain adequate blood levels to be an effective treatment. Physostigmine, furthermore, has relatively severe side effects, including nausea, vomiting and diarrhea (Coelho and Birks, 2001).

Over the past decade, several reversible, relatively long acting, orally administered, centrally acting AChE inhibitor agents have been marketed to alleviate the symptoms of Alzheimer's disease (e.g. Wolfson et al., 2002). These AChE inhibitors include donepezil, rivastigmine and metrifonate (Clegg et al., 2002; Inglis, 2002; Morris et al., 1998; Rosler, 2002; Wolfson et al., 2002). Despite their relative success in delaying the progression of Alzheimer's disease, these agents have only recently been considered as potential treatments for nerve agent exposure (Janowsky et al., 2004).

In our initial study we showed that acutely administered donepezil, alone or in combination with scopolamine, was able to counteract the hypothermic, hypokinetic and diarrhea-inducing effects of the irreversible anticholinesterase, DFP (a prototypic nerve agent) in hypercholinergic Flinders Sensitive Line rats (Janowsky et al., 2004). The addition of scopolamine was necessary to counteract the initial transient (1 h) hypothermic effects of donepezil itself. In the current study, we tested whether chronic treatment (10-day) with donepezil might block the effects of a subsequently administered toxic dose of DFP in standard Sprague–Dawley rats without causing significant side effects requiring the co-administration of scopolamine. The objective was to confirm that the principle of protection afforded by drugs used to treat Alzheimer's disease against DFP toxicity could be applied to normal rats and the findings, therefore, would be relevant to normal humans, not just a subgroup who are more sensitive to cholinergic agents, such as depressed individuals (Janowsky et al., 1994).

2. Materials and methods

2.1. Animals

In this experiment, male Sprague–Dawley (SD) rats (Charles-River, Raleigh, NC) were obtained at 70 days of age (300 g) and allowed to adapt to the local conditions before the experiment began 7–10 days later. The rats were housed in groups of 3 in polycarbonate cages under standard housing conditions (22 °C, 50% humidity) and a 12:12 light/dark cycle (lights on from 0700 to 1900). The experiments reported in this study were approved by the UNC Institutional Animal Care and Use Committee and were carried out according to the NIH Guide for the Care and Use of Laboratory Animals (NRC, 1996).

2.2. Drugs

DFP was obtained from Sigma Corporation (St. Louis, MO). It was dissolved in peanut oil at a concentration of 1.0 mg/ml and injected intramuscularly at a dose of 1.25 mg/kg. Donepezil (5.0 mg) tablets were obtained and were crushed and suspended in isotonic saline at a concentration of 2 mg/ml. Donepezil was injected IP at a dose of 2.0 mg/kg.

2.3. Design

2.3.1. Experiment 1: acute donepezil study

Four experimental groups consisting of 6 to 8 rats each were established. Each rat was pretreated with donepezil (2 mg/kg) i.p. or saline vehicle and 30 min later each was injected i.m. with DFP (1.25 mg/kg) or peanut oil vehicle. Thus the four treatment groups were vehicle–vehicle (VV), vehicle–DFP (VF), donepezil–vehicle (DV) or donepezil–DFP (DF).

2.3.2. Experiment 2: chronic donepezil study

Five experimental groups consisting of 6 to 8 rats each were used. Each rat received a pretreatment regimen (10 consecutive days) of i.p. injections followed by an acute i.m. injection of DFP or DFP vehicle (peanut oil). Experimental groups were: (1) vehicle (i.e. saline) injections for 10 days followed by acute vehicle injection (VV); (2) 2.0 mg/kg donepezil injections for 10 days followed by acute vehicle injection (DV); (3) vehicle injections for 10 days followed by acute 1.25 mg/kg DFP injection (VF), (4) 2.0 mg/kg donepezil injections for 10 days followed by acute 1.25 mg/kg DFP injection (DF), (5) 2.0 mg/kg donepezil injections for 10 days followed by acute vehicle injection followed by acute 1.25 mg/kg DFP injection one day (24 h) later on Day 11 (DVF). This latter group was included to determine if the protective effects of chronic donepezil treatment could still be observed 24 h after the last donepezil injection.

2.4. Procedure

Baseline temperatures were recorded prior to any treatments using a thermistor probe connected to a telethermometer (Physiotemp, Clifton, NJ). For the acute donepezil study temperatures were recorded again at 1, 2, 4, and 6 h after the injection of DFP or DFP vehicle. The presence or absence of diarrhea was noted at each recording of temperature. Measurement of activity was obtained by placing the rats in the center of an open field apparatus (60 × 60 cm) and recording lines crossed in 1 min at 4 h after the injection of DFP or its vehicle.

For the chronic donepezil study, the rats were injected i.p. daily according to the above pretreatment design. Temperatures were taken 60 min after the 1st, 4th, and 7th donepezil or vehicle injections to determine whether tolerance might have developed to the hypothermic effects of donepezil. After the 10th injection, rats were given either vehicle or DFP either 30 min (first four groups) or 24 h (DVF group) later. Temperatures were taken by rectal thermistor probe at 1, 2, 4 and 6 h following DFP or DFP vehicle injection and the presence/absence of diarrhea was noted at each recording. Approximately 5 min after the 4-h post-DFP recording of temperature, the rats were placed in an open field apparatus (60 cm × 60 cm having 16 squares [10 cm × 10 cm]) and line crossings were recorded for 1 min.

2.5. Statistical analysis

The temperature data (decrease in °C) were initially subjected to a two-way mixed ANOVA, with treatment as the independent factor and time as the related factor. When this analysis revealed a significant interaction between treatment and time, subsequent one-way ANOVAs of the treatment effects were carried out at each time point. When significant ANOVAs were found, subsequent Tukey's protected *t* tests were carried out to determine which pairs of groups differed. A one-way ANOVA and follow-up Tukey's tests were also conducted to determine the effects of the treatments on locomotor activity at the 4-h time point. The incidence of diarrhea at the 4-h time point was analyzed by Fisher exact probability tests.

3. Results

3.1. Acute donepezil study

Acutely administered donepezil was able to counteract the hypothermia induced by DFP, with the most dramatic results being seen at 6 h, as illustrated in Fig. 1. The vehicle/vehicle (V/V), donepezil/vehicle (DV), and donepezil/DFP (DF) groups all showed minimal changes from baseline temperature (from 0.1 to 0.2 °C) at 6 h, while the vehicle/DFP (VF) group exhibited a mean decrease of 2.0+0.5 °C (Fig. 1). However, as reported earlier (Janowsky et al., 2004), acute donepezil administration had hypothermic effects of its own. The decreases in temperature shown by the vehicle-treated groups at 1 h was significantly less than those exhibited by the donepezil-treated groups (Fig. 1).

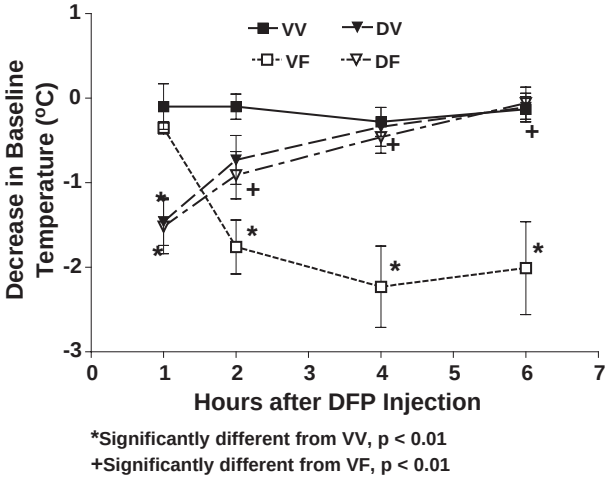

Fig. 1. Changes in temperature induced by DFP following pretreatment with acute donepezil or vehicle. Rats were pretreated with vehicle, and/or donepezil (2 mg/kg) 30 min prior to being treated with vehicle or DFP. Temperatures were then recorded 1, 2, 4, and 6 h later and related to previously recorded baselines. The values represent the mean ± S.E.M. change in temperature (°C) for 6–8 rats. Group codes: VV = vehicle–vehicle; DV = donepezil–vehicle; VF = vehicle–DFP; DF = donepezil–DFP.

Thus, the two-way ANOVA of the temperature effects over time revealed a significant group effect ($F[3,26]=10.27$, $p<0.001$) and a significant group × time interaction effect ($F[9,96]=15.74$, $p<0.00001$), but not a significant time effect ($F[3,96]=2.28$, $p>0.05$).

The incidence of diarrhea also varied with group and time. For example, the two donepezil-treated groups had the highest incidence of diarrhea at 1 h (5/7 for donepezil/vehicle and 8/8 for donepezil/DFP versus 0/7 for vehicle/vehicle and 2/8 for vehicle/DFP). In contrast, the vehicle/DFP group had the highest incidence of diarrhea at 4 h after the injection (7/8) and those of the other groups were significantly lower (0/8 for vehicle/vehicle, 1/7 for donepezil/vehicle, and 4/8 for donepezil/DFP). Thus, donepezil has substantial effects on diarrhea itself early on and seems somewhat protective against the diarrhea-inducing effects of DFP later on.

The vehicle/DFP group was the least active behaviorally 4 h after the injections, crossing only 10.4±2.2 lines. All of the other groups were equally more active (20.5±2.8 for vehicle/vehicle, 19.9±2.0 for donepezil/vehicle, and 18.2±1.6 for donepezil/DFP) and the ANOVA confirmed significant group differences ($F[3,26]=5.03$, $p<0.01$).

3.2. Chronic donepezil study

There was a significant decrease in temperature after acute treatment with donepezil (Day 1: 1.41±0.20 °C versus 0.41±0.07 °C for the vehicle-treated group ($t=4.49$, $p<\pm0.001$), but not after chronic treatment (Day 4: 0.53+0.08 °C versus 0.68+0.09 °C; $t=1.17$, NS; Day 7: 0.31+0.08 °C versus 0.29+0.1 °C; $t=0.15$, NS). Thus, tolerance rapidly developed to the hypothermic effects of donepezil.

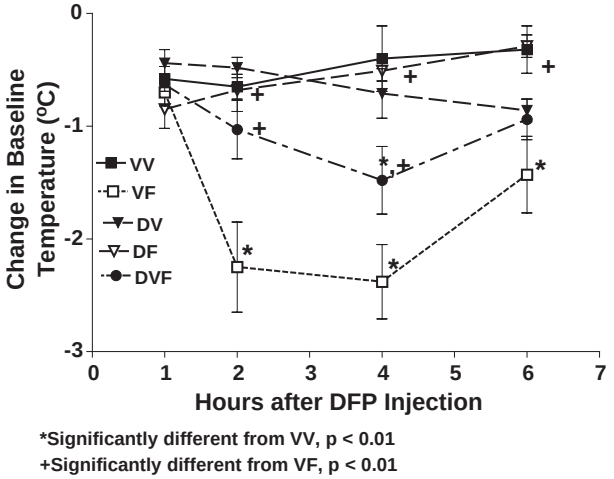

Fig. 2. Changes in temperature induced by DFP following pretreatment with chronic donepezil or vehicle. Rats were pretreated with vehicle, and/or donepezil (2 mg/kg) for 10 days 30 min or 24 h prior to being treated with vehicle or DFP. Temperatures were then recorded 1, 2, 4, and 6 h later and related to previously recorded baselines. The values represent the mean± S.E.M. change in temperature (°C) for 6–8 rats. Group codes: VV=vehicle–vehicle; DV=donepezil–vehicle; DF=donepezil–DFP; VF=vehicle–DFP; DVF=donepezil–vehicle–DFP.

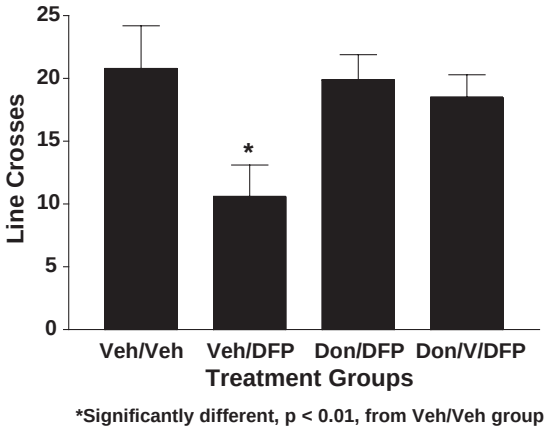

Fig. 3. Effects of chronic donepezil pretreatment on hypoactivity induced by acute DFP. Rats were treated according to the schedule given in Fig. 1. At 4 h after the injection of DFP or vehicle, the rats were placed in an open field arena for 1 min and line crosses were counted. Data represent the means±S.E.M. for 6–8 rats. *Significantly different from VV group according to Tukey's test.

Fig. 2 illustrates the effects of 10 days of pretreatment with donepezil on the hypothermic effects of DFP. The differences among the groups vary depending upon the time course. Thus, although there was a highly significant treatment effect ($F[4,40]=137.29$, $p<0.0001$), and a marginally significant time effect ($F[3,120]=2.64$, $p=0.05$), there was also a significant treatment × time interaction ($F[12,120]=3.08$, $p<0.01$). Importantly, chronic donepezil pretreatment protected against the hypothermic effects of DFP seen at the later time points (Fig. 2).

This protective effect was confirmed in the measures of locomotor activity (Fig. 3; $F[3,23]=3.99$, $p<0.02$). Only the vehicle/DFP group had significantly lower activity than the vehicle/vehicle group.

Finally, the incidence of diarrhea was highest in the vehicle/DFP group, with 4 out of 8 rats exhibiting diarrhea at 2 and 4 h, respectively, after treatment with DFP. There was no diarrhea in any of the other groups at 4 h and only 1 and 2 rats for the donepezil/DFP and donepezil/vehicle/VFP groups respectively at 2 h. These results suggest that the donepezil pretreatments were counteracting the toxic effects of DFP.

4. Discussion

The acute donepezil experiment established that acute donepezil treatment could significantly counteract the late-occurring hypothermic, hypokinetic and diarrhea-inducing effects of acute DFP in Sprague–Dawley (SD) rats, thereby confirming the results obtained in the hypercholinergic FSL rats (Janowsky et al., 2004). However, the early acute effects of donepezil were substantial, making this acute strategy problematic unless a centrally active anticholinergic

was also given, as reported previously (see Janowsky et al., 2004). Consequently, the effects of a chronic donepezil treatment regimen were evaluated.

The results suggest that chronic donepezil treatment, given for 10 days, effectively reduced the hypothermic, activity-inhibiting, and diarrhea-inducing effects of DFP without having any effects on its own. Thus, donepezil, a centrally acting anti-AChE agent used in the treatment of Alzheimer's disease, has a parallel effectiveness to physostigmine, another centrally active anti-AChE agent (Lim et al., 1988, 1991; Philippens et al., 2000). However, unlike physostigmine, which can have many unwanted side effects such as lethargy, nausea, vomiting and diarrhea (Coelho and Birks, 2001) and which has a relatively short half-life, donepezil has been used in treating Alzheimer's patients with relatively few (11%) side effects (Inglis, 2002; Pratt et al., 2002) and has a relatively long half-life of up 70 h (Roman and Rogers, 2004). Furthermore, when donepezil is given chronically, there is tolerance development to its hypothermic effects so there are no demonstrable hypothermic effects of donepezil itself at the time of the DFP challenge (Fig. 2), as was the case with acute treatment (Janowsky et al., 2004; Fig. 1).

It is important to note that the current study did not use lethal or supralethal doses of DFP. Thus, it is not certain that pretreatment with donepezil can prevent death, as does physostigmine (Philippens et al., 2000). However, it is likely that death arising from AChE inhibitor poisoning, like hypothermia and hypoactivity, involves the same cholinergic mechanisms. Therefore, one would predict that chronic donepezil pretreatment would also protect against the lethal effects of other AChE inhibitors, including nerve agents, without causing initial toxic additive effects. Of particular note in the present study, chronically administered donepezil offered protection against the effects of DFP, even when there was a relatively long (24 h) interval between the former and latter injections. This finding suggests that donepezil may still have an impact on DFP 24 h after its last dose is given, possibly due its long half-life (Roman and Rogers, 2004).

This study could have been more complete if brain AChE values were reported. However, the literature indicates that we would expect that the peak inhibition of AChE induced by 2 mg/kg donepezil to be about 40–50% (Geerts et al., 2005; Kaasinen et al., 2002). Thus, effective protection against DFP can occur with approximately 50% inhibition of AChE.

There are some limitations to the practical application of the above findings. Acutely administered donepezil had initial cholinergic effects (hypothermia and diarrhea). These effects can be blocked by low doses of scopolamine (Janowsky et al., 2004), which can be given initially in a chronic regimen of donepezil. Alternatively, it is likely that starting at a low dose and slowly escalating the dose of donepezil during chronic treatment may induce tolerance development to its effects and thus avoid potential side effects (e.g. Chippendale et al., 1972; Overstreet, 1974). Such an escalating strategy was not used in this experiment because it was considered that a constant dose strategy would be more easily translated to the human situation.

There are limitations to abstracting data from animal studies to effects in humans. These include dosing, sensitivity and metabolic differences. Also, all AChE inhibitors do not respond equally to various antagonists. Thus, the positive result for treatment of one AChE inhibitor may not apply to others. Nevertheless, we have shown that donepezil given chronically, can block the hypothermic and other effects induced by DFP in SD rats without causing serious side effects of its own. Thus, these treatments have potential for blocking the central and peripheral toxic effects of nerve agents. Whether other agents used to treat Alzheimer's disease have similar prophylactic effects must be properly tested.

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