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ORIGINAL ARTICLE

# Memantine and Its Combination with Acetylcholinesterase Inhibitors in Pharmacological Pretreatment of Soman Poisoning in Mice

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## Abstract

Nerve agents pose a real threat to both the military and civil populations, but the current treatment of the poisoning is unsatisfactory. Thus, we studied the efficacy of prophylactic use of memantine alone or in combination with clinically used reversible acetylcholinesterase inhibitors (pyridostigmine, donepezil, rivastigmine) against soman. In addition, we tested their influence on post-exposure therapy consisting of atropine and asoxime. Pyridostigmine alone failed to decrease the acute toxicity of soman. But all clinically used acetylcholinesterase inhibitors administered alone reduced the acute toxicity, with donepezil showing the best efficacy. The combination of memantine with reversible acetylcholinesterase inhibitors attenuated soman acute toxicity significantly. The pretreatment administered alone or in combinations influenced the efficacy of post-exposure treatment in a similar fashion: (i) pyridostigmine or memantine alone did not affect the antidotal treatment, (ii) centrally acting reversible acetylcholinesterase inhibitors alone increased the antidotal treatment slightly, (iii) combination of memantine with reversible acetylcholinesterase inhibitors increased the antidotal treatment more markedly. In conclusion, memantine alone failed to decrease the acute toxicity of soman or increase post-exposure antidotal treatment efficacy. The combination of memantine with donepezil significantly increased post-exposure effectiveness (together 5.12, pretreatment alone 1.72). Both drugs, when applied together, mitigate soman toxicity and boost post-exposure treatment.

**Keywords** Soman · Memantine · Pyridostigmine · Donepezil · Rivastigmine · Mice

## Introduction

Nerve agents or other highly toxic organophosphorus compounds (OPs) pose a real threat to both the military and civil populations since they can be employed in wartime or terrorist attacks. After exposure, OPs irreversibly bind to acetylcholinesterase (AChE, EC 3.1.1.7) and disrupt its physiological function: degradation of acetylcholine in the synaptic clefts. The accumulated neurotransmitter overstimulates both types of cholinergic receptors, leading to headaches, glandular hyperexcretion, urinary and fecal incontinence, and seizures; death commonly occurs due to acute respiratory insufficiency (Bajgar 2004; Colovic et al. 2013).

Antidotal therapy against nerve agents comprises mostly anticholinergics (atropine) and anticonvulsive drugs (diazepam). In addition, AChE reactivators (briefly oximes) can restore the physiological function of AChE (Bajgar 2004; Colovic et al. 2013). Despite all efforts, the effectiveness of oxime therapy is still limited by (i) aging of the enzyme-inhibitor complex, which impedes AChE reactivation, and (ii) poor distribution of oximes into tissues such as the brain (Chambers et al. 2020; Kassa 2019; Lorke et al. 2008). This especially hampers counteracting the centrally acting agents like soman (pinacolyl methylfluorophosphonate). This makes soman of particular interest for testing (i) new treatment strategies focused on central nervous system (CNS) protection and (ii) pretreatment strategies.

Pretreatment strategies represent the medical countermeasures administered relatively shortly before the actual exposure to nerve agents. Its administration should increase (i) resistance of humans against OPs and (ii) effectiveness of post-exposure therapy (Bajgar et al. 2009). Prophylactic AChE reversible inhibitors (AChEIs) can protect AChE against nerve agent–induced irreversible damage (Bajgar et al. 2009; Layish et al. 2005; Patocka et al. 2006). The armed forces generally accept pyridostigmine bromide as a pretreatment agent

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of choice (Karasova et al. 2020a, b). Based on its physicochemical properties, we assume it acts mostly in the periphery. However, the protection of cholinergic and glutamate receptors in the brain is paramount. The prevention of nerve agent–induced excitotoxicity and dysfunction ameliorates (i) the signs and symptoms of the acute cholinergic crisis, (ii) development of secondary neuronal damage, and (iii) long-term neuropsychiatric and neurological disorders (Chen 2012; Shih and McDonough 1997). Figure 1 depicts a simplified scheme of the pathological cascade in the brain after OP exposure (inspired by Chen 2012).

To augment the pretreatment strategies, centrally acting reversible AChEIs, commonly used in Alzheimer's disease (AD), such as donepezil or rivastigmine, should replace pyridostigmine. In addition, other centrally acting reversible AChEIs such as physostigmine were evaluated as promising prophylactic drugs against nerve agent poisoning (Leadbeater et al. 1985; Miller et al. 1993; Myhrer and Aas, 2016). The glutamate neurotoxicity associated with the cholinergic crisis could be mitigated by another anti-AD drug — memantine (non-competitive *N*-methyl-D-aspartate receptor antagonist). Stojiljkovic et al. (2019) demonstrated the prophylactic potential of memantine in soman-poisoned rats; memantine also alleviates dichlorvos toxicity in the same species (Zhou et al. 2005). To our knowledge, the efficacy or potential risk of using memantine with commonly used centrally acting AChEI drugs (donepezil and rivastigmine) has not been evaluated.

This study aims to evaluate the influence of memantine alone or in combination with reversible AChEI (pyridostigmine, donepezil, or rivastigmine) on the resistance against soman acute toxicity and the therapeutic efficacy of the currently used antidotal treatment (asoxime in combination with atropine) in soman-poisoned mice.

## Material and Methods

### Animals

Male NMRI mice weighing 18–22 g were purchased from VELAZ (Prague, Czech Republic). They were kept in an air-conditioned room (22 ± 2 °C and 50 ± 10% relative humidity), with lights from 7:00 a.m. to 7:00 p.m. and ad libitum access to standard food and tap water. The mice were divided into groups of six animals ($n = 6$). Mice are used in our studies for many years. Therefore, mice were used in this study to compare our new results with previously published results.

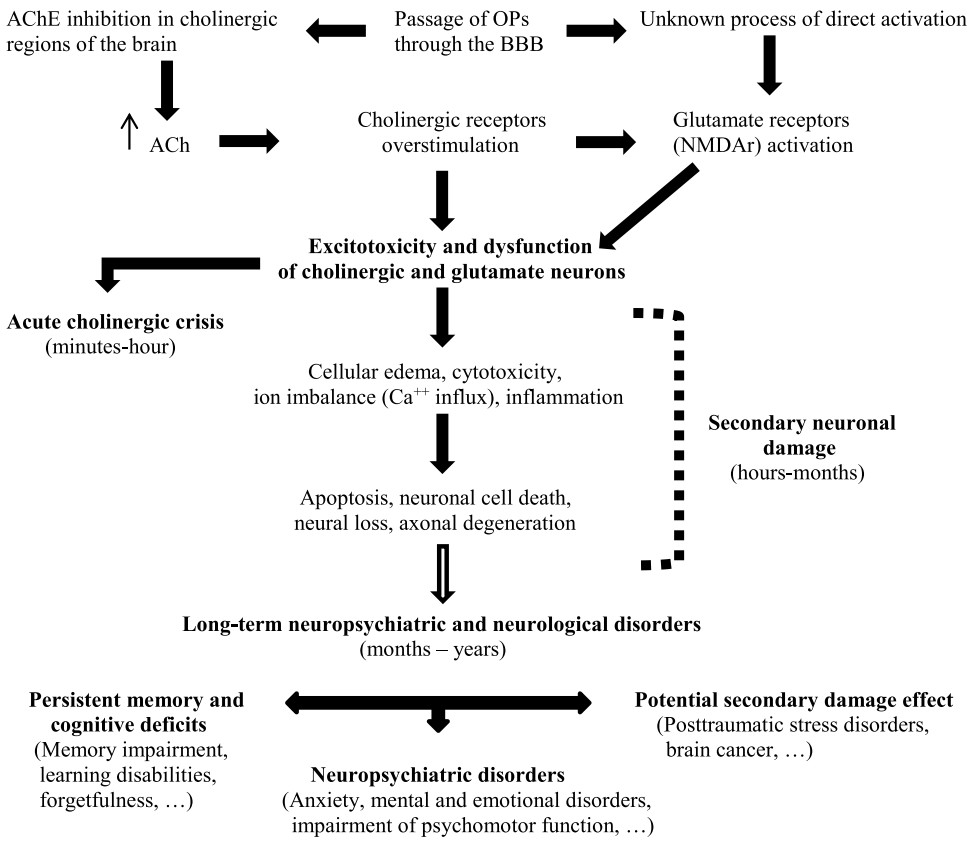


**Fig. 1** Pathological cascade in the brain after higher OP dose exposure (AChE acetylcholinesterase, OPs organophosphates, BBB blood–brain barrier, ACh acetylcholine, NMDAr *N*-methyl-D-aspartate receptor)

## Chemicals

Soman was obtained from the Military Technical Institute in Brno (Czech Republic) and was 90.0% pure. Its purity was assayed by acidimetric titration. All other drugs and chemicals of analytical grade were obtained commercially and used without further purification. All substances were administered intramuscularly (i.m.) at a volume of 10 mL/kg body weight (b.w.).

## Evaluation of Prophylactic Efficacy of Pyridostigmine and Anti-AD Drugs

Memantine was administered at a dose of 20 mg/kg based on literature (Jackson et al. 2019). Pyridostigmine was administered at a dose of 0.162 mg/kg, donepezil at a dose of 2.65 mg/kg, and rivastigmine at a dose of 1.2 mg/kg. Doses of reversible AChEIs were established based on previous studies (Bruins Slot et al. 2003; Kassa et al. 2012; Kosasa et al. 1999) and were attributed to approximately 40% brain AChE inhibition (Misik and Kassa 2014). The doses of reversible AChEIs were chosen to be sufficiently safe to avoid potential adverse drug reactions in both peripheral and central compartments.

Pyridostigmine and anti-AD drugs, or their respective combinations, were administered i.m. 30 min before i.m. soman injection. Soman-induced toxicity was evaluated by assessing its $LD_{50}$ value and its 95% confidence interval using probit-logarithmical analysis of death occurring within 24 h after administering soman at five different doses with six animals per dose (Tallarida and Murray 1987). The efficacy of tested prophylactic drugs was expressed as the protective ratio ($LD_{50}$ value of soman in pretreated mice/$LD_{50}$ value of soman in non-pretreated mice). The differences between $LD_{50}$ values were significant when $p < 0.05$ (Tallarida and Murray 1987).

## Evaluation of the Influence of Pyridostigmine and Anti-AD Drugs on the Therapeutic Efficacy of Antidotal Treatment

The pretreatment (memantine, reversible AChEIs, and their combinations) was administered i.m. 30 min before soman to evaluate the impact of pyridostigmine and anti-AD drugs on antidotal efficacy. All doses corresponded with the previously described part of our study. Antidotal (post-exposure) treatment consists of asoxime in a dose corresponding to 5% of its $LD_{50}$ (33.6 mg/kg) and atropine (10 mg/kg). Both were administered together via i.m. injection 1 min after soman intoxication. Soman-induced toxicity was evaluated as described previously (Tallarida and Murray 1987). Two protective ratios were calculated to evaluate the potential influence of pretreatment on overall antidotal efficacy: (i) protective ratio *A* ($LD_{50}$ value of soman in pretreated mice with antidotal treatment/$LD_{50}$ value of soman in non-pretreated mice without antidotal treatment), (ii) protective ratio B ($LD_{50}$ value of soman in pretreated mice with antidotal treatment/$LD_{50}$ value of soman in non-pretreated mice with antidotal treatment). The differences between $LD_{50}$ values were significant when $p < 0.05$ (Tallarida and Murray 1987).

## Results

The behavioral changes in animals exposed to various treatment regimens are summarized in Table 1. The mice suffered from salivation, respiratory difficulties, muscular twitching and fibrillation, and ultimately tonic–clonic convulsions. The pretreatment of soman poisoning was able to slightly postpone the onset of soman-induced toxic signs and symptoms and slightly diminish their intensity (see Table 1). To compare the time of onset of soman-induced toxic signs and symptoms and the intensity of toxic signs and symptoms, the behavioral changes in mice were observed after

**Table 1** Soman-induced toxic signs and symptoms

| Pretreatment | Signs and symptoms | Time of onset (min) |
|---|---|---|
| — | Salivation, respiratory difficulties, intensive muscular twitching, opisthotonus, tonic–clonic convulsions | 1–2 |
| **Memantine** | Salivation, respiratory difficulties, tremor, moderate muscular twitching, opisthotonus | 2–3 |
| **Pyridostigmine** | Salivation, respiratory difficulties, tremor, moderate muscular twitching, opisthotonus | 2–3 |
| **Donepezil** | Salivation, respiratory difficulties, tremor, moderate muscular twitching, opisthotonus, an activity decreasing | 2–3 |
| **Rivastigmine** | Salivation, respiratory difficulties, tremor, moderate muscular twitching | 1–2 |
| **Memantine + pyridostigmine** | Salivation, mild respiratory difficulties, tremor, mild muscular twitching | 2–3 |
| **Memantine + donepezil** | Salivation, mild respiratory difficulties, tremor, mild muscular twitching, an activity decreasing | 2–3 |
| **Memantine + rivastigmine** | Salivation, mild respiratory difficulties, tremor, mild muscular twitching, opisthotonus | 1–2 |

**Table 2** Prophylactic effect of pyridostigmine and anti-AD drugs on the $LD_{50}$ value of soman in mice. Statistical significance: $^{*}p < 0.05$ (between non-pretreated and pretreated mice)

| Pretreatment | $LD_{50}$ (μg/kg) ± 95% CL | Protective ratio |
|---|---|---|
| — | 110.3 (81.2–123.0) | — |
| Memantine | 130.6 (92.3–163.7) | 1.18 |
| Pyridostigmine | 100.8 (84.8–111.7) | 0.91 |
| **Donepezil** | **148.5 (129.0–173.7)*** | **1.35** |
| Rivastigmine | 123.0 (105.3–163.8) | 1.11 |
| **Memantine + pyridostigmine** | **169.9 (130.3–221.5)*** | **1.54** |
| **Memantine + donepezil** | **175.6 (144.3–198.6)*** | **1.59** |
| **Memantine + rivastigmine** | **156.3 (134.5–200.8)*** | **1.42** |

Protective ratio ($LD_{50}$ value of soman in pretreated mice/$LD_{50}$ value of soman in non-pretreated mice)

administration of soman at the dose corresponding to its $LD_{50}$ value in each group.

Table 2 shows the overall prophylactic efficacy of pyridostigmine, anti-AD drugs, and their combinations. While peripherally acting pyridostigmine failed to decrease acute soman toxicity, centrally acting rivastigmine and memantine were slightly effective. On the other hand, donepezil decreased the acute toxicity of soman significantly. Combined pretreatment with memantine and AChEIs increased pretreatment efficacy regardless of the AChEI used (see Table 2).

Table 3 gives data on the effect of prophylactic pyridostigmine, anti-AD drugs, and their combinations on the post-exposure treatment of soman toxicity. Pyridostigmine and memantine alone failed to improve the overall therapeutic outcome. Centrally acting reversible AChEIs ameliorated the antidotal treatment only slightly with the best results in donepezil. The pretreatment combinations boosted the overall therapeutic efficacy against soman markedly; memantine and donepezil proved the most effective combination.

## Discussion

Effective treatment of acute soman intoxication still proves difficult. The causal antidotes (oximes) often fail because of the rapid aging of the AChE-soman complex (Alozi and Rawas-Qalaji 2020; Antonijevic and Stojiljkovic 2007; Marrs et al. 2006; Mercey et al. 2012). Therefore, appropriate pretreatment regimes may improve the overall treatment efficacy against soman as well as other highly toxic OPs. The commonly used reversible AChEIs (e.g., pyridostigmine) can inhibit/protect some of the AChE with the subsequent spontaneous recovery of AChE activity, boosting the available pool of active enzyme (Bajgar et al. 2009; Lorke and Petroianu 2019).

The potential benefits or risks of long-term pyridostigmine therapy remain unknown. The relatively small therapeutic window also limits its practical use. The safe dose for humans is ineffective against centrally acting OPs in

**Table 3** The influence of prophylactic pyridostigmine and anti-AD drugs on the overall therapeutic efficacy against soman. Statistical significance: $^{*}p < 0.05$ (protective ratio *A*), $^{x}p < 0.05$ (protective ratio *B*)

| Pretreatment | Treatment | $LD_{50}$ (μg/kg) ± 95% CI | Protective ratio *A* | Protective ratio *B* |
|---|---|---|---|---|
| — | — | 98.3 (75.7–112.9) | — | — |
| — | HI-6Atropine | 291.4 (222.1–368.5)* | 2.96 | — |
| Memantine | HI-6Atropine | 291.1 (247.2–344.0)* | 2.96 | 1.00 |
| Pyridostigmine | HI-6Atropine | 297.9 (245.6–361.2)* | 3.03 | 1.02 |
| Donepezil | HI-6Atropine | 349.2 (320.1–403.3)* | 3.55 | 1.20 |
| Rivastigmine | HI-6Atropine | 331.4 (277.0–398.1)* | 3.37 | 1.14 |
| Memantine + pyridostigmine | HI-6Atropine | 332.3 (242.1–460.7)* | 3.38 | 1.14 |
| **Memantine + donepezil** | HI-6Atropine | **503.2 (406.3–625.9)*$^{x}$** | **5.12** | **1.73** |
| Memantine + rivastigmine | HI-6Atropine | 367.5 (223.1–493.8)* | 3.74 | 1.26 |

Protective ratio *A* ($LD_{50}$ value of soman in pretreated mice with antidotal treatment/$LD_{50}$ value of soman in non-pretreated mice without antidotal treatment), protective ratio *B* ($LD_{50}$ value of soman in pretreated mice with antidotal treatment/$LD_{50}$ value of soman in non-pretreated mice with antidotal treatment) Combination of memantine and donepezil is statistically significant in both cases, as protective ratio *A* and protective ratio *B*

most cases (Dunn et al. 1997). Our study confirms the negligible prophylactic value of pyridostigmine: the protective ratio was 0.92 as pretreatment and 1.02 with post-exposure therapy. Previously published studies bring similar results (Bajgar et al. 2019; Kassa et al. 2017). This limitation may be related to insufficient brain penetration. Numerous alternative AChEIs have also been investigated for possible anti-OP effectiveness (Bajgar et al. 2019; Kassa et al. 2012; Lorke et al. 2011; Lorke and Petroianu 2019). Physostigmine is one of the promising centrally acting AChEIs. It can protect nerve agent–poisoned animals against neurological symptoms and severe behavioral incapacitation (Myhrer and Aas, 2016). Many investigators have found physostigmine to be superior to pyridostigmine in protecting against nerve agents (Leadbeater et al. 1985; Miller et al. 1993). However, it was described that physostigmine can cause undesirable behavioral side effects in high doses; for example, administration of physostigmine results in impaired shuttle-box performance and increased acoustic startle response (Philippens et al. 1996).

The commonly used anti-AD drugs (donepezil and rivastigmine) seem as viable alternatives (Karasova et al. 2020a, b). Their toxicity, brain distribution, and adverse effects have been thoroughly explored (Bures et al. 2020, 2021; Korabecny et al. 2019; Nguyen et al. 2021; Rong et al. 2021; Valis et al. 2017; Zemek et al. 2014). While pyridostigmine administered alone failed, donepezil decreased soman's acute toxicity significantly (the protective ratio 1.35).

The acute cholinergic crisis, which springs from cholinergic receptor overstimulation, predominates in the first minutes after intoxication. This impairment induces high glutamate release leading to widespread hyper-excitation that causes generalized seizure activity (McDonough and Shih 1997). As it was previously described, administration of soman "convulsive" dose leads to brain lesions observed in the hippocampus, amygdala, and thalamus and consisted of neuron necrosis, dropout, gliosis, astrocytosis, and vascularizations (Britt et al. 2000). Combining compounds with different neuroprotective mechanisms might reduce secondary neuronal damage. Memantine mitigates glutamate excitotoxicity via NMDA receptor antagonism (Marotta et al. 2020; Stojiljkovic et al. 2019). Memantine alone fails to terminate seizure activity because of cholinergic overstimulation (Jackson et al. 2019; Shih et al. 1999). However, it was shown that memantine could attenuate AChE inhibition and prevent myonecrosis and muscle fasciculation and other signs of cholinergic toxicity in rats when administered before soman, sarin, tabun, or VX exposure (Gupta and Dettbarn 1992; McLean et al. 1992). Of note, memantine reduces OP-induced cell death in various vulnerable brain regions such as the amygdala, thalamus, piriform cortex, hippocampus, and parietal cortex (Jackson et al. 2019). Moreover, memantine lowers levels of oxidative stress markers in the cerebrospinal fluid, especially non-protein thiols and 3-nitrotyrosine (Valis et al. 2019). Although we used the maximal recommended dose (20 mg/kg; Stojiljkovic et al. 2019), memantine alone as pretreatment decreased the toxicity of soman only slightly (the protective ratio 1.18) and grants little to no effect in the efficacy of post-exposure treatment (see Tables 2 and 3). A higher dose can induce severe adverse effects; the most common are motor hyperactivity, ataxia, and behavioral impairments (hyperexcitability, stereotypic movements, and convulsions) (Stojiljkovic et al. 2019). This narrow therapeutic window seriously limits its pretreatment utilization, especially when administered alone.

In the AD treatment, a connection between glutamatergic and cholinergic systems was observed. Both possess some implications in cognitive function (Parsons et al. 2013). In the moderate or severe stages of AD, the AChEI effect is supported by memantine. Together, they can synergistically and effectively tackle the AD pathological cascade (Marotta et al. 2020; Tariot and Federoff 2003). This approach may also be beneficial for the pretreatment of highly toxic OPs. Our study demonstrated the benefit of combining memantine with AChEI due to complementary effects (reversible inhibition of AChE and elimination of glutamate release). In all cases, this combination decreased acute soman toxicity significantly (protective ratio 1.42–1.59). The experiments dealing with the influence of prophylactic drugs on the efficacy of post-exposure antidotal treatment brought similar results. Contrary to Stojiljkovic et al. (2019), who described a non-significant improvement of similar post-exposure treatment by memantine, we proved that memantine did not affect the post-exposure treatment of soman poisoning (see Table 3).

On the other hand, the combination of memantine with AChEI increased the effectiveness of post-exposure treatment. Among them, the combination with donepezil gave the best results (protective ratio of 5.12). The explanation may relate to its pharmacodynamic properties: donepezil acts rapidly as reversible, mixed competitive, and non-competitive selective AChEI; the AChE/BChE ratio in humans is 405:1 (Zeb et al. 2017). Donepezil interacts with both the catalytic and peripheral binding sites, resulting in enhanced AChE inhibition (Cheung et al. 2012). Moreover, it also protects against (i) glutamate excitotoxicity via interaction with nicotinic ACh receptors (Takada-Takatori et al. 2006) — possible potentiation of memantine effect; (ii) neural damage via increase of AChE-R expression and inhibition of AChE-S expression (Nordberg 2006); (iii) oxidative stress via alteration of free radical output (Tsukada et al. 2000); and (iv) cerebral ischemia (Chen et al. 2006).

## Conclusion

The hypothetical memantine protection is based on (i) reduction of centrally mediated seizures due to non-competitive NMDA receptor antagonism with subsequent decrease of the glutamate-induced release of ACh (Lupp et al. 1992), (ii) protection of neuromuscular transmission against ACh-induced depolarization block following AChE inhibition due to its ability to inhibit the nicotinic receptor-sodium ionophore complex (Tsai et al. 1989), and (iii) partial protection of AChE against soman-induced irreversible inhibition (Stojiljkovic et al. 2019). Based on our results, the benefit of memantine administered alone was insufficient but, combined with AChEI, it is probably able to improve overall resistance against soman. Donepezil seems to be the best choice among selected AChEI. Its pharmacodynamic effects suitably complement the memantine central effect.

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**Author Contribution** Both authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by both authors. The first draft of the manuscript was written by J. Kassa, and both authors commented on precious versions of the manuscript. Both authors read and approved the final manuscript.

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**Availability of Data and Material** The data and material associated with this article can be found in the online version.

## Declarations

**Ethics Approval** All procedures and protocols used in the study were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Handling of experimental animals was approved by the Ethics Committee of the Faculty of Military Health Sciences in Hradec Králové (Czech Republic) by approval number 163135/2020–684800.

**Conflict of Interest** The authors declare no competing interests.

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