Antimuscarinics for the Treatment of Overactive Bladder: A Review of Central Nervous System Effects

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Antimuscarinic drugs commonly used to treat overactive bladder are often associated with central nervous system (CNS) side effects including cognitive dysfunction, memory impairment, dizziness, fatigue, and headache. New agents show reduced CNS penetrance and better selectivity for the M3 muscarinic receptor. However, changes associated with aging may lead to alterations in blood–brain barrier permeability. Therefore, use of antimuscarinics in the elderly or in patients with Alzheimer's disease presents a significant challenge. This review highlights muscarinic receptor distribution and function in the CNS, provides a description and incidence of CNS side effects with therapy, offers information specific to currently available agents, and describes the use of antimuscarinics in special populations including children, the elderly, and patients with Alzheimer's disease.

Introduction

Overactive bladder is defined by the International Continence Society as "urgency, with or without urge incontinence, usually with frequency and nocturia" [1]. The condition affects approximately 17% of the adult population worldwide [2,3] and has a tremendous impact on quality of life [4] and health care economics [5]. Pharmacotherapy with antimuscarinic drugs is the most common form of medical management for overactive bladder. However, efficacy with these agents is limited and side effects are frequent [6••].

Antimuscarinic therapy for the treatment of overactive bladder may trigger a wide range of central nervous system (CNS)-specific side effects because of the crucial role muscarinic receptors play in the CNS. CNS side effects may include alterations in memory and cognitive functioning, dizziness, somnolence, asthenia, insomnia, nervousness, headache, confusion, sleep disturbances, and overt psychotic behavior. Unfortunately, there is no consistent definition of "CNS effects," which often precludes comparison among drug trials. For example, the prescribing information for trospium [7] lists "headache" under the category of "nervous system disorders." Conversely, the prescribing information for tolterodine [8] treats "headache" as a "general" symptom.

Because the prevalence of overactive bladder increases with age [9], and because elderly patients are more likely to exhibit many of these symptoms or to have dementia prior to drug therapy, CNS side effects associated with antimuscarinic therapy for overactive bladder deserve special consideration. Furthermore, patients may be ingesting several drugs possessing anticholinergic properties. Therefore the "total anticholinergic load" must be considered. Indeed, the geriatric literature specifically states that certain anticholinergics prescribed by urologists such as hyoscyamine and oxybutynin are inappropriate in the elderly [10].

In recent years, new antimuscarinic agents approved for clinical use demonstrate more favorable pharmacokinetics or receptor binding selectivity that potentially alleviate these CNS side effects. Comparator trials designed to detect differences in side effects or to examine subtle or long-term changes in cognition in high-risk groups are lacking. These shortcomings, however, have not prevented the marketing of some new drugs as possessing improved CNS side-effect profiles based on either limited penetration into the brain or muscarinic receptor selectivity.

This review highlights the current state of knowledge or uncertainty regarding CNS side effects of antimuscarinics used to treat overactive bladder. Topics include an overview of muscarinic receptor distribution and function in the CNS, description and incidence of CNS side effects with therapy, information specific to currently available agents, and use of antimuscarinics in special populations including children, the elderly, and patients with Alzheimer's disease.

Muscarinic Receptors in the Central Nervous System

Five muscarinic receptors are known: M1 to M5. These subtypes have been characterized by receptor affinity studies, second messenger signaling systems, and by G-protein coupling [11]. M1, M3, and M5 receptors all couple with Gq/11 and ultimately lead to release of calcium from the sarcoplasmic reticulum. M2 and M4 receptors, conversely, are coupled to Gi proteins and their activation leads to inhibition of adenylate cyclase. In the brain, all five receptor subtypes have been identified, but their levels of expression and distribution vary widely. In general, M1 receptors are expressed in areas involved in memory and cognitive functioning, including the neocortex, hippocampus, and neostriatum, and M2 receptors are expressed throughout the brain. In contrast, M3 receptors have very low levels of expression in the brain. M4 and M5 receptors are also expressed in the brain but have a more limited distribution [12•]. Studies with selective antagonists and knockout mice demonstrated that the M1 and M2 receptors are important for cognitive functioning, whereas the M3 receptor is not considered important in this regard [13]. The role of acetylcholine in cognition and memory is more complex than previously believed based merely on receptor distribution. Data from selective muscarinic receptor knockout mice indicate that M1 receptors are necessary for cognitive processing between the hippocampus and cortex. Moreover, postsynaptic M2 receptors are required for behavioral flexibility and learning. M2 autoreceptors, when activated, increase acetylcholine release and improve memory. These observations suggest that CNS effects of nonselective muscarinic receptor blockade are not always predictable.

Besides their unique patterns of receptor selectivity, the CNS effects of the currently available antimuscarinics are also related to their pharmacokinetic properties, including molecular size, polarity, lipophilicity, specificity for the P-glycoprotein efflux pump, protein binding, and drug half-life [12•]. Limited access to, and effect within, the CNS are expected with larger molecular size, poor lipophilicity, strong charge polarity, abundant protein binding, short half-life of active metabolites, and poor specificity for the P-glycoprotein efflux pump. In contrast, small molecular size, strong lipophilicity, neutral charge, limited protein binding, and long half-life of active metabolites would promote easy access to and effect within the CNS. As an example, metabolism of tolterodine by the cytochrome P-450 system produces a metabolite that has antimuscarinic activity similar to that of the parent compound. Therefore, the CNS penetrance of each compound must be considered.

General Central Nervous System Effects

In general, significant CNS-related side effects have not been observed in the new second-generation antimuscarinic agents, darifenacin [14] and solifenacin [15,16], with results similar to placebo in clinical trials. In contrast, older antimuscarinics, especially oral oxybutynin, are associated with higher rates of CNS side effects. However, it must be noted that oxybutynin has been approved for use in the United States for more than 30 years, and trospium has been available in Europe for 20 years. The new antimuscarinic agents have been on the market only since 2004, which limits the time for reporting of adverse events [17,18]. In recent trials of oxybutynin and tolterodine, dizziness, somnolence, and asthenia occurred most frequently, with incidences ranging from about 2% to 5% [19,20]. These percentages may be artificially low based only on patient complaints and exclusion of subjects at higher risk, including elderly patients or those with early dementias. It is well recognized that patients are often unaware of cognitive dysfunction or changes in memory. Indeed, according to product information provided in the package inserts, total CNS-related side effects occur much more frequently for oxybutynin (18%) versus all other available agents (< 5%).

One of the most troubling CNS side effects associated with antimuscarinic therapy is memory impairment. This is especially of concern because the prevalence of overactive bladder increases with age, and many elderly patients with overactive bladder may already have memory impairment secondary to Alzheimer's disease or other conditions. Reversible memory impairment is well established for oxybutynin [21••]. Furthermore, in rodent models treated with high-dose oxybutynin, significant alterations in learning and memory processing were observed [22]. However, limited reports of this condition have also occurred with tolterodine [23]. Tolterodine likely exerts its effects directly and through the actions of an active 5-hydroxymethyl metabolite. This active metabolite is converted from the parent drug via the CYP2D6 enzyme and is significantly less lipophilic. Thus, it is expected to have limited penetration into the CNS. However, in approximately 7% of the population, this enzyme is lacking, potentially giving the more lipophilic parent compound better access to the CNS. Furthermore, oxidative metabolism by the P-450 system declines with aging, which may contribute to higher serum levels than expected of the parent compound in the elderly [24]. Although memory impairment has not been reported with the other commonly used antimuscarinics in the treatment of overactive bladder, large-scale studies specifically powered to detect a small but significant change are lacking. Although drug surveillance and monitoring are in place, the system is woefully inadequate and underfunded to provide a safety net for the public.

In addition, rare hallucinations and episodes of frank psychosis have been reported with both oxybutynin [25] and tolterodine [26]. The mechanism responsible for this effect is not entirely clear. However, interaction between cholinergic and dopaminergic neurons in

the brain stem [27] may be causally important. Direct evidence for CNS effects of antimuscarinics has been shown in electroencephalogram (EEG) studies of young healthy volunteers [28]. In this study, subjects were treated on a single day with three consecutive doses of oxybutynin, tolterodine, trospium, or placebo and then subjected to EEG testing under various conditions. Oxybutynin was associated with the most pronounced CNS effects compared with the minimal effects of tolterodine and trospium. It must be noted, however, that EEG changes are common with many agents and their clinical significance is difficult to interpret.

Specific Central Nervous System Effects

First-generation antimuscarinics

Oxybutynin chloride (Ditropan XL; Ortho-McNeil Pharmaceutical, Titusville, NJ) [29], one of the more commonly used antimuscarinics for the treatment of overactive bladder, is a non–receptor selective tertiary amine that is highly lipophilic, has small molecular size (molecular weight = 393.9), and is neutrally charged. The drug binds preferentially to M1 and M3 receptors (K_i [inhibition constant ratio] = 12.3 for M3/M2 and 1.5 for M3/M1). This agent easily penetrates the CNS and is the agent to which newer agents with improved pharmacokinetic properties and more receptor selectivity have traditionally been compared. For extended-release oxybutynin (Ditropan XL), the drug half-life is 13.2 hours, and it is metabolized extensively by the liver such that less than 1% is excreted unchanged in the urine. Metabolism in the liver is accomplished by CYP34A, part of the cytochrome P-450 system. Therefore, concomitant use of agents that inhibit the cytochrome P-450 system, such as ketoconazole, results in a twofold increase in the plasma concentration of oxybutynin. Significant CNS side effects (reported in ≥ 5% of patients) include only somnolence and dizziness, which occurred in a total of 18% of patients. These CNS effects were seen in dose escalation trials (n = 580) in which patients received escalating drug doses up to 30 mg/d. When patients received a static dose of only 10 mg/d, somnolence and dizziness occurred in a total of 6% of patients. Other CNS side effects occurred with less frequency (< 2% of treated patients) and included insomnia, nervousness, and confusion. Overdose with more than 100 mg of extended-release oxybutynin has been reported associated with the CNS effects of memory loss, stupor, disorientation, and agitation. However, no deaths have been reported. Site of administration is also important as CNS effects for the oxybutynin patch (Oxytrol; Watson Pharma, Corona, CA) were similar to placebo in clinical trials [30].

Tolterodine tartrate (Detrol LA; Pfizer, New York, NY) [8], like oxybutynin, is a tertiary amine. However, its lipophilicity is dramatically reduced (> 30-fold) in comparison with oxybutynin, and it has larger molecular size (molecular weight = 475.6). It is not M3 selective (K_i = 3.6 for M3/M2, K_i = 0.6 for M3/M1). Liver metabolism via the CYP2D6 enzyme of the cytochrome P-450 system creates a 5-hydroxymethyl metabolite that has antimuscarinic activity similar to the parent compound. Because 7% of the white population and 2% of the African American population lacks this enzyme, markedly higher serum concentrations of the parent compound with insignificant concentrations of the 5-hydroxymethyl metabolite are observed. Serum concentrations are elevated by as much as 50% in healthy elderly volunteers; however, no differences in clinical effects or side effects have been observed. Lower doses (2 mg versus 4 mg) are recommended in patients with hepatic and renal insufficiency. CNS side effects in phase 2 and 3 clinical trials (n = 537 vs placebo = 536) include headache (6% vs 4% placebo), fatigue (2% vs 1% placebo), dizziness (2% vs 1% placebo), somnolence (3% vs 2% placebo), and anxiety (1% vs 0% placebo). Reports of confusion, disorientation, memory impairment, and hallucinations have also been reported but occurred in less than 1% of treated patients.

Trospium chloride (Sanctura, Esprit Pharma, East Brunswick, NJ; and Indevus Pharmaceuticals, Lexington, MA) [7] is a large quaternary amine (molecular weight = 427.97) with reduced lipophilicity and high polarity. Therefore, this agent has limited access to the CNS. It is poorly M3 selective (K_i = 1.3 for M3/M2, K_i = 1.5 for M3:M1). Protein binding occurs (> 50%) when the drug achieves therapeutic serum concentration. The half-life of this compound is approximately 20 hours. The mechanism of its metabolism is unknown; however, metabolism by cytochrome P-450 system enzymes does not occur. In phase 2 and 3 clinical trials, CNS side effects were reported in patients treated with the drug (n = 591 vs placebo = 590) and included headache (4.2% vs 2.0% placebo) and fatigue (1.9% vs 1.4% placebo). Additional rare postmarketing CNS effects such as syncope, hallucinations, and delirium have also occurred but may not have had a direct relationship to drug usage [7].

Second-generation antimuscarinics

Darifenacin hydrobromide (Enablex; Novartis, Basel Switzerland) [31] is an M3-selective antimuscarinic compound with large molecular size (molecular weight = 507.5). Receptor affinity studies demonstrate somewhat higher (nine- to 12-fold) affinity for M3 compared with M1 and M5 but a 59-fold higher affinity for M3 compared with M2 and M4. Serum half-life is 12.43 hours but it is significantly longer in the subset of patients lacking the CYP2D6 enzyme responsible for metabolism of this drug. In the serum, the overwhelming majority of the drug (98%) is protein bound. Lower dosing is advised in patients with hepatic insufficiency; however, despite higher serum levels in women and elderly persons, dose adjustment in these populations is not recommended. In phase 3 clinical trials (n = 671 vs placebo = 388), CNS

side effects including dizziness (2.1% vs 1.3 placebo) and asthenia (2.7% vs 1.3% placebo) occurred with greater frequency than with placebo only at the higher dose (15 mg). No other CNS side effects have been reported with darifenacin administration.

Solifenacin succinate (VESIcare; Astellas Pharma, Tokyo, Japan, and GlaxoSmithKline, Brentford, UK) [32] has M3 selectivity similar to oxybutynin (K_i = 12 for M3/M2, K_i = 2.5 for M3/M1) with a higher molecular weight (480.55). Metabolism occurs in the liver via the CYP3A4 enzyme of the cytochrome P-450 system. Caution is advised when using this drug in patients with hepatic or renal insufficiency. In phase 3 clinical trials (n = 1811 vs placebo = 1216), CNS side effects occurring with greater frequency than placebo include depression (1.2% vs 0.8% placebo), fatigue (2.1% vs 1.1% placebo), and dizziness (1.9% vs 1.8% placebo). No cases of acute overdose with solifenacin have been reported [32]. Table 1 highlights the pharmacokinetic and CNS effects of the antimuscarinic agents discussed here.

Special Patient Populations

The elderly

Clinicians must be aware of the various ways that antimuscarinics can adversely affect the elderly. First, hepatic and renal clearance of drugs are reduced with aging. Second, as mentioned, cognitive changes and frank dementias are more common. Third, the average Medicare patient takes seven to nine prescription drugs, so the likelihood of drug–drug interactions increases. Lastly, many of these drugs already have anticholinergic properties, so the total anticholinergic load is substantial. For these reasons, geriatric societies have published lists of drugs (eg, the Beers list) that are to be avoided in the elderly, and among these drugs are hyoscyamine and oxybutynin, two antimuscarinics [10].

In healthy subjects older than 50 years, antimuscarinic therapy was found to have a significant effect on delayed recall [21••]. In this study, patients were randomly assigned to receive extended-release oxybutynin, darifenacin, or placebo for 3 weeks. A battery of cognitive tests was administered at baseline and after each week of treatment. Oxybutynin treatment was associated with a significant decrease in delayed recall and a moderate decrease in immediate recall; however, memory effects were seen only at doses of 15 mg or higher daily. This is important because a typical starting dose for extended-release oxybutynin is 10 mg daily. The decline in delayed recall was considered equivalent to 10 years of normal aging. Conversely, the effects of darifenacin on memory were similar to placebo. Interestingly, based on the results of self-rated memory testing, subjects treated with oxybutynin were unaware of memory deficits. This last finding is extremely important for elderly patients in whom the side effect of memory impairment may go unreported because the patients themselves may not be aware of the problem.

Another study also examined the effects of the commonly used antimuscarinics oxybutynin, tolterodine, and trospium on sleep in healthy volunteers older than 50 years. In this investigation, patients were randomly assigned to receive oxybutynin, tolterodine, trospium, or placebo 2 hours before sleep and were subjected to polysomnography testing in a sleep laboratory. Oxybutynin reduced duration of rapid eye movement (REM) sleep by 14% and tolterodine reduced duration of REM sleep by 15% compared with placebo. Trospium did not alter the duration of REM sleep. Of note, when subjects were asked to rate the quality of sleep, no differences were identified. In the elderly population, this lack of awareness is important and likely places elderly patients at increased risk for falls and cognitive impairment. These same investigators performed a similar study in younger volunteers and found mild, nonstatistically significant reductions in REM sleep for oxybutynin and tolterodine (8% and 5%, respectively), with no change identified for trospium [33].

Recently, results from a large-scale, longitudinal cohort study [34•] identified mild cognitive impairment in 80% of patients taking antimuscarinics for overactive bladder compared with 35% in age-matched controls who were not on this therapy. The authors concluded that antimuscarinic therapy was associated with a fivefold increased risk for mild cognitive impairment; however, progression to frank dementia was not observed in any patients, suggesting that the effects of this therapy may be reversible with cessation of drug therapy.

In the elderly, heightened CNS effects are expected, as alterations in the blood–brain barrier with a resultant increase in drug permeability are believed to occur with aging. In a rodent model of cold brain injury, investigators found significantly more cerebral water content in old versus young animals, showing that aging is associated with increased permeability of the blood–brain barrier in response to injury [35]. In another model, rodents were exposed to both restraint stress and neurotoxic chemical exposure, as a potential model of Gulf War syndrome. Disruption of the blood–brain barrier and neuronal cell death were prominent in areas important for cognitive functioning and memory processing, including the cingulate cortex, the dentate gyrus, the thalamus, and the hypothalamus [36]. Potential mechanisms for increased permeability associated with this model include opening of tight junctions, epithelial shrinkage, and vascular dilation. Thus, improvements in pharmacokinetics of new antimuscarinic agents (ie, increased molecular size and decreased lipophilicity) may be irrelevant in the setting of age- or injury-related alterations in blood–brain barrier permeability.

Children

With the exception of oxybutynin, data regarding the widespread use of antimuscarinic agents to treat overactive bladder in children are not available. However, in this patient population, CNS side effects may be more pronounced. In a study of children with spina bifida, CNS side effects were observed in six of 101 patients (6%) treated with oral or intravesical oxybutynin. Side effects included drowsiness, hallucinations, and cognitive changes. However, this was not a placebo-controlled trial. It is interesting to note that CNS effects were observed even in children treated with intravesical oxybutynin. In a study of children with diurnal incontinence, oxybutynin therapy did not result in cognitive impairment or CNS side effects [37]. However, this was a much smaller study.

Patients with Alzheimer's disease

The use of antimuscarinic therapy to treat overactive bladder in patients with Alzheimer-type dementia raises important safety questions. Alzheimer's disease is a neurodegenerative disease that accounts for more than 50% of all cases of dementia. The prevalence of this disease increases dramatically with age, affecting less than 1% of the population aged 60 to 64 years but as many as 33% older than 85 years [38•]. It is associated with aggregates of β-amyloid plaques and neurofibrillary tangles in the cerebral cortex. There is a known genetic susceptibility for this disease as promoter mutations associated with increased expression of amyloid precursor protein (APP) have been identified in patients and animal models of Alzheimer's disease [38•].

Most clinicians are unaware that besides influencing cognition and memory processing, muscarinic receptors likely play key roles in the pathophysiology of Alzheimer's disease. Plaque formation occurs after various secretases cleave the APP at specific sites. Cleavage of APP by β- and γ-secretases forms amyloidogenic products that are more prone to aggregation and plaque formation. In contrast, cleavage by α-secretase produces products that are nonamyloidogenic (Fig. 1). Studies suggest that activation of M1 and M3 muscarinic receptors may increase the nonamyloidogenic activity of α-secretase, whereas activation of the M2 muscarinic receptor may increase the amyloidogenic activity of β- and γ-secretases. Thus, muscarinic receptors are important in the pathophysiology of Alzheimer's disease, and therapies that alter the precise balance of receptor activation or inactivation may either promote or prevent this condition. Furthermore, widespread use of acetylcholinesterase inhibitors to treat Alzheimer's disease tempts us to speculate that antimuscarinic therapies could potentially worsen disease progression. However, combining antimuscarinics to treat overactive bladder and acetylcholinesterase inhibitors to treat Alzheimer's disease has been used successfully in patients with both conditions [39].

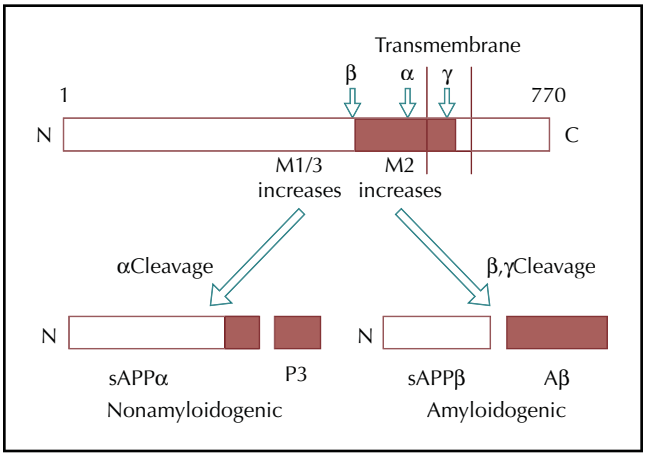

Figure 1. Processing of amyloid precursor protein (APP). APP is cleaved differentially by α-, β-, and γ-secretases to form nonamyloidogenic products (*left*) or amyloidogenic products (*right*). Activation of M1 and M3 receptors promotes increased α-secretase activity and may lead to increased production of nonamyloidogenic products. Activation of M2 receptors promotes increased β- and γ-secretase activity and may lead to increased production of amyloidogenic products. In theory, antimuscarinics used to treat overactive bladder may alter the balance of receptor activation and may worsen or even improve amyloid plaque deposition.

This theoretical concern was heightened by an autopsy investigation in which the brains of patients with Parkinson's disease were examined [40]. The study found that long-term use of antimuscarinics in this patient population was associated with higher rates of amyloid plaque and neurofibrillary tangle formation. This was the first study to suggest the possibility of permanent neurodegenerative changes associated with long-term antimuscarinic therapy in humans. In fairness, many of the drugs investigated in this study (amitriptyline, benztropine, imipramine, orphenadrine, oxybutynin, and trihexyphenidyl) are not typically used to treat overactive bladder. In addition, Parkinson's disease is associated with neurodegenerative changes and the study was retrospective and not powered to detect a change. Lastly, the ability to accurately identify drug effects in this heterogeneous patient population should be viewed with skepticism. Nevertheless, the theoretical concern exists and changes may take years to develop.

In our own laboratory, we studied the effects of long-term oxybutynin administration on a transgenic murine model of Alzheimer's disease (Tg2376). This doubly transgenic strain expresses human mutations in the presenilin and APP genes and leads to amyloid plaque formation by 6 months of age [41,42]. To our surprise, we found that animals treated with oxybutynin showed reduced plaque deposition, reduced APP production, and improved cognitive functioning in comparison with animals treated with placebo control [43,44]. Interestingly, the improvement in cognitive function was observed only for female Alzheimer's disease mice treated with oxybutynin. This speaks to the possibility of beneficial effects of estrogen on hippocampal

functioning and is supported by evidence that estrogen, acting through a presynaptic estrogen receptor β, may enhance function of the M2 autoreceptor [45].

Conclusions

Central nervous system side effects with antimuscarinic agents used for the treatment of overactive bladder include cognitive dysfunction, memory impairment, dizziness, fatigue, and headache. However, rarer and more severe effects including hallucination and frank psychosis have also been reported. Incidence of these side effects is related to unique pharmacokinetic properties of available antimuscarinic agents. As such, agents that are non–receptor selective, have small molecular size, are lipophilic, and have a neutral charge are more likely to gain access to the CNS and cause untoward effects. Unfortunately, the blood–brain barrier may become "leaky" with age and brain injury, allowing easier access despite a safe pharmacokinetic profile. When used in the elderly and in patients with Alzheimer's disease, antimuscarinics are of particular concern; however, currently available data in these populations are mixed and do not allow for a clear statement regarding their safety and efficacy. The prudent approach in using antimuscarinics, especially in the elderly or cognitively impaired, is "start low and go slow" with regards to dosing. Eliminate other anticholinergic drugs if possible. Finally, if CNS alterations are a concern or if CNS side effects occur, the current array of antimuscarinics offers the opportunity to try agents that have more limited access to the CNS (trospium) or more M3 selectivity (darifenacin, M3:M1 = 9.3, M3:M2 = 59.2). In between are agents with less CNS access (tolterodine) or with slightly more M3 selectivity (solifenacin, M3:M1 = 2.5, M3:M2 = 12.6).

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