ORIGINAL

H_1 Antihistamines and Benzodiazepines. Pharmacological Interactions and their Impact on Cerebral Function

J Montoro[1], J Bartra[2], J Sastre[3], I Dávila[4], M Ferrer[5], J Mullol[6], A del Cuvillo[7], I Jáuregui[8], A Valero[2]

[1]Allergy Unit, Arnau de Vilanova University Hospital, Faculty of Medicine, Catholic University of Valencia "San Vicente Mártir", Valencia, Spain
[2]Allergy Unit, Pneumology and Respiratory Allergy Department, Hospital Clínic (ICT), Barcelona, Spain
[3]Allergy Department, Jiménez Diaz Foundation, Madrid, Spain
[4]Immunoallergy Department, Salamanca University Welfare Complex, IBSAL, Salamanca, Spain
[5]Allergology Department, Navarra University Clinic, Pamplona, Spain
[6]Rhinology Unit and Olfactory Clinic, Otorhinolaryngology Department, Hospital Clínic (ICT), Barcelona, Spain
[7]Dr. Lobatón Clinic, Cadiz, Spain
[8]Allergy Department, Basurto University Hospital, Bilbao, Spain

Resumen

Los antihistamínicos (AH) han sido clasificados en primera y segunda generación atendiendo a sus propiedades farmacocinéticas, características estructurales y efectos adversos. Los efectos ejercidos sobre el sistema nervioso central (SNC) vienen determinados fundamentalmente por su capacidad de atravesar la barrera hematoencefálica y fijarse a los receptores H1 centrales. Las benzodiacepinas (BZD) son fármacos con efectos ejercidos en el SNC tras su unión al lugar específico de los receptores GABA tipo A. A dosis bajas, las BZD tienen efectos ansiolítico y anticonvulsivante, y a medida que la dosis se incrementa aparecen la sedación, amnesia y finalmente la inconsciencia. Se han realizado diversos estudios acerca de la posible interacción entre las BZD y los AH H1 con atención especial a su efecto sobre el SNC. En unos casos han sido estudios para valorar la seguridad de dicha asociación y en otros casos el objetivo ha sido distinto: se ha observado si la administración conjunta tiene un mejor resultado terapéutico en patología relacionada con síndrome ansioso o insomnio. De forma general puede afirmarse que los AH de primera generación interaccionan con las BZD incrementando los efectos sedantes de éstas. Sin embargo, los AH de segunda generación no incrementan sus efectos sedantes, lo que los convierte en los fármacos electivos para tratar rinitis/rinoconjuntivitis alérgicas y urticarias en pacientes que reciban conjuntamente BZD.

Palabras clave: Antihistamínicos H1 1ª generación. Antihistamínicos H1 2ª generación. Benzodiacepinas. Sistema gabaérgico. Sistema histaminérgico.

Abstract

Antihistamines (AH) have been classified into first and second generation according to their pharmacokinetic properties, structural characteristics and adverse effects. The effects on the central nervous system (CNS) are determined basically by their capacity to cross the hematoencephalic barrier and attach to central H1 receptors. Benzodiazepines (BZD) are drugs with effects on the CNS following their union to the specific location of GABA receptors type A. At low doses, the BZD have sedative and anticonvulsive effects, and as the dose increases it leads to sedation, amnesia and finally unconsciousness. Various studies have been made on the possible interaction between the BZD and the AH H1 with special attention to their effect on the CNS. In some cases these were studies to assess the safety of this association and in others, the aim was different: to see if their joint administration gives a better therapeutic result in pathology related with anxiety syndrome or insomnia. In general it can be said that first generation AH interact with the BZD increasing the sedative effects of the latter. However, second generation AH do not increase these sedative effects, which makes them the chosen drugs to treat allergic rhinitis/rhino-conjunctivitis and urticaria in patients also receiving BZD.

Key words: Antihistamines H1 1st generation. Antihistamines H1 2nd generation. Benzodiazepines. GABAergic system. Histaminergic system.

Introduction

Antihistamines

Antihistamines (AH) are inverse agonist drugs of the H_1 histaminergic receptor. They bind to it and stabilise it in its inactive conformation, thus preventing the histamine from binding to it and acting as an inflammatory mediator [1, 2]. They directly reduce the allergic inflammation by acting on the H_1 receptors of the sensitive nerves and small blood vessels, and indirectly through the infra-regulation of the nuclear-κβ receptor, reduction of presentation of the antigen, chemotaxis and molecules of cellular adhesion. They also stabilise the mastocyte membrane, probably through a diminution of the intracellular concentration of calcium [2].

AH have been classified into first and second generation depending on their pharmacokinetic properties, structural characteristics and adverse effects.

Their effects on the central nervous system (CNS) are determined fundamentally by their capacity to cross the hematoencephalic or blood-brain barrier (BBB) and attach to the central H_1 receptors (RH_1). The capacity to cross the BBB will depend on the lipophilic quality of the molecule and its affinity with P-glycoprotein (P-gp).

P-gp is a protein which actively regulates the transport across the cellular membrane of molecules important from the biological viewpoint, such as hormones, nutrients and xenobiotic substances, both in their introduction into and extraction from the cell, independently of their concentration gradient on both sides of the cell membrane. The extraction of substances is carried out through the energy produced by hydrolysis of a molecule of adenosine triphosphate (ATP) [3]. It is found on the luminal surface of the renal tubular cells, hepatocytes, enterocytes and on the endothelial surface of the testicular and cerebral vessels [4]. The cerebral capillaries have hermetic intercellular unions and a relative absence of transendothelial conduits for the passive diffusion of soluble molecules. However, these are not the only components of the hematoencephalic barrier, also forming part of it are the microglia, astrocytes, pericytes (essential in maintaining the structure of the hermetic intercellular unions) and the neurons themselves. All these structures together are called the neurovascular unit, essential to the correct functioning and integrity of the CNS [5].

AH of the first generation are lipophilic and have little affinity with P-gp, in contrast to those of the second generation, considered substrata of P-gp and less lipophilic. The distinction based on the different molecular weight (at less molecular weight there is more theoretical facility in crossing the BBB) becomes less and less important. For example, desloratadine has a molecular weight (338.9) similar to hydroxyzine (347.9) but its permanence in the cerebral tissue after its administration is different.

The studies which have to be carried out to classify an antihistamine as non-sedative are based on three aspects:

a) Subjective effect of sleepiness (its presence).
b) Objective studies which assess possible alterations in cognitive and psychomotor functions.
c) Studies of the occupation of central RH1 by positron emission tomography (PET), which has become the chosen technique for studying the penetration of antihistamines in cerebral tissue. This technique allows a correlation of the occupation of central RH1 with psychometric and functional studies [6]. The greater the occupation of RH1 the more affected are the studies of psychometrics and cerebral functions.

Although the latter two are particularly important, all three must be present to obtain the cataloguing [7, 8].

Chen et al. demonstrated that the penetration in cere¬bral tissue of a first generation antihistamine was 5.5 times greater than one of the second generation [9].

Benzodiazepines

Benzodiazepines (BZD) are allosteric modulator drugs of the inhibitory postsynaptic signal induced by gamma-amino-butyric acid (GABA) after its union to the specific place of GABA type A receptors ($GABA_A$) which contain the subunits α_1, α_2, α_3 or α_5, in combination with one subunit β and one γ_2 . The exact place of union is located between subunits α and γ.

BZD do not interact with $GABA_A$ receptors containing a subunit α_4 or α_6.

They strengthen the action of GABA at the level of the $GABA_A$ receptor, increasing the entry of chlorine into the interior of the cell and all this results in a inhibitory postsynaptic signal.

Other types of drugs can also unite to the $GABA_A$ receptor, such as anticonvulsants, barbiturates, some anaesthetics and also ethanol [10].

There are different types of BZD, fundamentally differentiated by their pharmacokinetic characteristics, more specifically by their degree of lipophilia and their elimination half life (including their active metabolites) [11]. The most extensive classification distinguishes 3 categories of BZD in accordance with their elimination half life in short, medium and long duration [12]:

a) BZD of short action (< 6 hours): midazolam, triazolam.
b) BZD of medium action (6-24 hours): alprazolam, lorazepam.
c BZD of long action (>24 hours): diazepam.

However, it must be taken into account that the elimination half life only reflects the time required for the drug to be eliminated, but that it has absolutely no correlation with the sedative effect. The start and duration of the action are more related with the lipophilia of the drug, so that the greater the lipophilia the faster the action starts, due to greater absorption and diffusion through the hematoencephalic barrier and, in turn, its duration will be shorter due to a broader distribution in the adipose tissue, so promoting a redistribution of the drug from the brain [11].

BZD have multiple therapeutic applications, the more usual being: sleep disorders (insomnia), anxiety disorders, agoraphobia, alcohol withdrawal, epileptiform disorders, muscular relaxation, premedication for anaesthetic and intraoperational sedation. At low doses BZD have an anxiolytic and anticonvulsant effect, and as the dose increases sedation, amnesia and finally unconsciousness appear. The effect is dependant on the dose [13].

They are metabolized by liver cytochrome P450 isoenzymes, principally by CYP3A4 and CYP2C19, their metabolism being able to be affected in the event of joint administration with CYP3A4 inhibitors. Given that some of their active metabolites have a slower metabolism than the primary active principle, the duration of the effect of many benzodiazepines has little relation with the elimination half life of the drug primarily administered, as has been described earlier.

Their adverse effects are related with depression of the CNS functions and of motor abilities. Their intensity and incidence increase with age [12].

An important characteristic of these drugs is the development of tolerance. In general it is accepted that the chronic use of BZD leads to compensatory changes at CNS level, that is, the $GABA_A$ receptor develops a hypo-response with the continued use of these drugs as a result of mechanisms of adaptation in the receptor itself, intracellular mechanisms or changes in other neurotransmitter systems of (serotonin, dopamine and acetylcholine), that is, this is a complex process in which multiple mechanisms can participate simultaneously to produce different degrees of tolerance, depending on the effect studied and the drug administered [10].

In order to reduce the adverse effects of BZD drugs have been developed with a greater affinity on the subunit α_1 of the $GABA_A$ receptor, the most extensively distributed in the brain of all the α subunits, and also especially important in the sedation induced by BZD. Mutations in subunit α_1 produce insensitivity to the sedative effects of diazepam, but the anxiolytic effects, muscular relaxation and deterioration of psychomotor functions are maintained. These new drugs are called "z-drugs" and include zolpidem, zaleplon, zoplicone and eszoplicone. They are hypnotics, not benzodiazepines, with an agonist effect on the place of union of BZD in the $GABA_A$ receptor which contains the subunit α_1. They are differentiated among themselves principally by their length of action and, therefore, by their clinical applications. Zoplicone has a long action so it is used to maintain sleep, while zaleplon is of short action and is used to induce it. On rare occasions phenomena of tolerance to this group of "z-drugs" are developed [12, 14].

The histaminergic system

Although the histamine is normally understood as an inflammatory mediator secreted by mastocytes and basophils in the immediate phase of the allergic reaction, it must not be forgotten that the histamine is also an endogenous neurotransmitter. There are approximately 64,000 neurons producing histamine, located exclusively in the tuberomammillary nucleus of the posterior hypothalamus, from where they send projections to the rest of the brain [15, 16]. Other neurotransmitters expressed in this nucleus include GABA, galanin, encephalines, TRH and substance P [17].

The morphological characteristics of the histaminergic system are similar to other biogenic amine systems (norepinephrine, serotonin), that is, a compact neuronal nucleus from which numerous fibres depart in all directions. The histamine interacts on the CNS with H_1-H_2-H_3-H_4 specific receptors, distributed throughout the CNS, to produce the various activities. The distribution of the RH1 in the human brain is very broad, being found principally in the frontal, temporal and occipital cortex, the cingulate, the caudate nucleus, the putamen and the thalamus [18]. This distribution differs according to sex, with greater density of RH1 in all areas in women [19].

The histamine at cerebral level is involved in many functions, such as the sleep-wake cycle, attention, memory and learning, excitation and regulation of the appetite [6]. It acts as a central regulator of the general cerebral activity. Recently it was given a neuroprotective role in cases of cerebral ischemia and neurodegenerative disorders [20].

The histaminergic system interacts with other systems and with other neuropeptides to produce the following actions:

a) Modulating the release of acetylcholine by acting on the magnocellular basal nucleus which provides the cortex with the majority of its cholinergic innervation. The local application of histamine reduces the cholinergic tone through H_3 receptors, causing difficulty in learning and cognitive deterioration, while the administration of thioperamide (antagonist of the H3 receptor) improves the capacity of retention and memory [21].
b) Modulating the acquisition of emotional memory by acting on the basolateral amygdala, principally the memory of situations associated with fear. However, in relation to its action on the hippocampus the results are disparate. We can state that the action of histamine affects learning and memory, even in a contradictory form, without being able to establish whether it facilitates or inhibits it [22].
c) Modulating the state of alertness; histaminergic neurons are activated at low level during sleep and at high level during attention and wakefulness. It interacts with secretory neurons of orexin (peptide neurotransmitter which affects the state of alertness, a deficiency of which produces narcolepsy). This reciprocal interaction (histamine-orexin) has a synergic effect on control of the maintenance of a state of alertness, the histaminergic system being principally responsible for cortical activation and cognitive activities, while the orexinergic system is

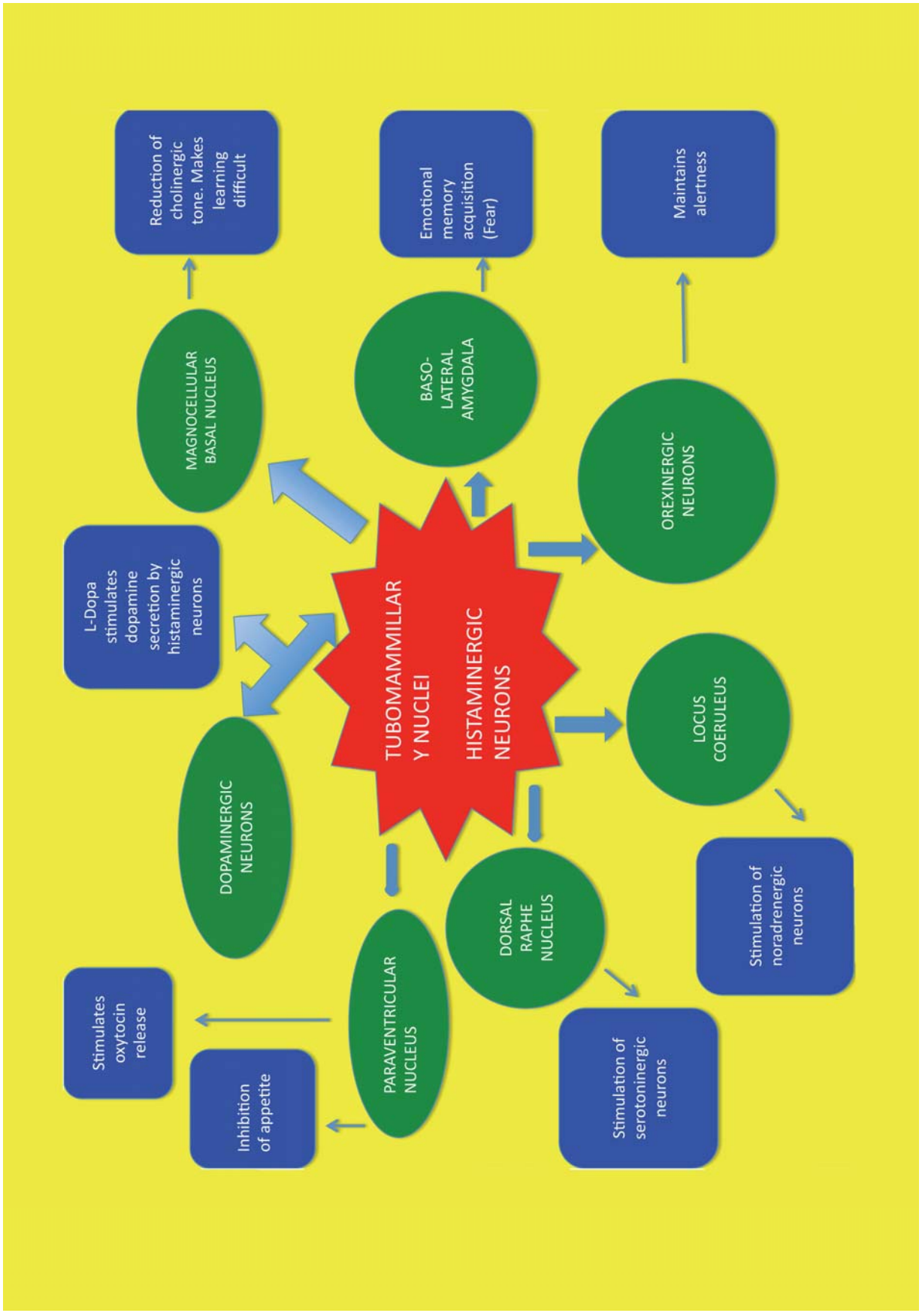

Figure 1. Scheme of the histaminergic system

more involved in behaviour while awake, including muscular tone, position, movement, ingesting food and emotive reactions [17]. It interacts, in turn, with the principal cerebral noradrenergic nucleus (the locus coeruleus). It has been found that the administration of histamine in this nucleus increases the excitation of its neurons [23].

It also interacts to excite the serotoninergic neurons of the dorsal raphe nucleus by the activation of RH_1 [24, 25].

d) Regulating the food intake; histamine is one of the neurotransmitters that suppress appetite. Noradrenalin, present in the paraventricular hypothalamic nucleus, stimulates the ingesting of food. It has been shown that histamine inhibits the release of noradrenalin in the nerve endings of the paraventricular nucleus to suppress the appetite [26].
e) Controlling the secretion of oxytocin in various physiological situations, including childbirth and breast-feeding. The histamine acts on the paraventricular hypothalamic nucleus, increasing the intranuclear and systemic release of oxytocin [27].
f) Interaction with the dopaminergic system. The histaminergic neurons are excited by L-Dopa, they express dopa-decarboxylase and release dopamine. Given that in Parkinson's disease the histaminergic system remains relatively intact and its neuronal prolongations extend densely towards the zones most deteriorated by the disease (*substantia nigra* or striated substance), the histaminergic system is being studied as a future therapeutic objective, with dopaminergic agonist agents [28].

The Figure 1 shows a schematic sketch of the histaminergic system.

Tagawa et al. [29] demonstrated, in a study carried out with PET and comparing ebastine with chlorpheniramine, that a higher occupation of cerebral RH_1 is correlated with higher plasma levels of chlorpheniramine, and in turn with the deterioration of the cognitive function, but the same does not happen with ebastine (with its active metabolite, carebastine). The ebastine 10 mg occupied approximately 10% of RH_1, while the chlorpheniramine 2 mg exceeded 50%. This greater penetration into the tissues by first generation AH was later demonstrated also with those of the second generation, specifically cetirizine, which shows an occupation of 13% with a dose of 10 mg and 25% with a dose of 20 mg, although it could not be correlated with a subjective sensation of sleep in this case [30].

Second generation or non-sedative AH occupy between 10 and 30% of the cerebral RH1, with the exception of fexofenadine which does not occupy [31].

For an antihistamine to be considered as non-sedative, its occupation of central receptors must not be over 20% when administered at the maximum recommended dose [7].

Nevertheless, Hindmarch et al. [32] introduced the concept of non-sedative AH for those which had no effects on the CNS when administered at doses greater than those recommended in the technical file, leaving the term scarcely sedative for those which did not show effects on the CNS at the maximum recommended dose but did do so at larger doses.

The central manifestations appear after the occupation of more than 50% of the cerebral RH1 [29], although some authors say that it requires occupation of 60% or even 70% [33].

The gabaergic system

GABA is the principal neurotransmitter inhibitor of the brain in mammals. It acts through 3 different receptors, $GABA_A$, $GABA_B$ and $GABA_{A\text{-}\rho}$ (previously called $GABA_C$).

GABAA is the most important from the physiological viewpoint, it has various functions in the CNS, is involved in neurological disorders, in the response to drugs and it regulates the majority of the rapid brain inhibitory impulses. As has been said before, this receptor is composed of several subunits (pentamer). The most numerous receptors are those which contain 2 subunits α, 2 subunits β and one subunit $\gamma 2$ (2α, 2β, $\gamma 2$), these being the principal place of binding of benzodiazepines and being key factors in their therapeutic effect, given their broad distribution throughout the cerebral cortex, substantia nigra, hippocampus and cerebellum [13, 34]. In contrast to $GABA_A$, the $GABA_B$ receptors transmit the slow inhibitory responses [34]. The $GABA_{A\text{-}\rho}$ regulate responses to changes in the light intensity in the retinal cells [35].

Adequate functioning of the cerebral cortex depends on two types of neurons [36]:

a) Activator neurons, these are projection neurons which send their axons to distant parts of the cortex and subcortical areas. They have pyramidal form neuronal bodies and use glutamate as a neurotransmitter.
b) Inhibitor neurons, these are neurons which take the form of local inter-neuronal circuits, whose axons are not projected to the substantia alba. They use GABA as a neurotransmitter. They account for approximately 20-30% of the total neurons of the cerebral cortex.

These gabaergic inter-neurons, in spite of their lower numbers, play a key role in the maintenance of a dynamic balance between excitation and inhibition [37]. There are various subgroups which are distinguished by their form (basket, candelabrum, bipolar, bouquet), molecular markers (proteins fixing calcium, neuropeptides), and for their functional properties and interneuron connections (rapid stimulation, stimulation in bursts, regular stimulation) [38]. The GABA released in presynaptic terminations causes hyperpolarization of the postsynaptic membrane, generating an inhibitory effect. The basic function of this mechanism is the suppression or modulation of the excitatory cortical pyramidal activity, so that the gabaergic inhibition is necessary for normal cortical function [36].

However, it is important to take into account that

the GABA effects differ according to the period of development of the CNS. In the embryonic period and shortly after birth, the GABA produces depolarization of the postsynaptic membrane with its consequent excitation, thus contributing, through trophic factors, to the genesis of cerebral activation networks, motoneuronal development in both the brain and the spinal medulla, leading to the suggestion that in the early phases of development the GABA is the principal excitatory neurotransmitter [36, 39]. Given its importance in the developing brain, the dysfunction of gabaergic neurons has been seen as an etiological factor in various CNS development disorders such as epilepsy, hyperalgesia and allodynia [40]. Studies with quantitative autoradiography, which have examined the density and distribution of subunits of gabaergic receptors, have shown a reduction of the gabaergic function in the hippocampus of patients with disorders in the spectrum of autism and epilepsy, and a loss of inhibitory interneurons in brains affected by epilepsy. Data obtained from animal models and *post-mortem* human samples suggest that the gabaergic neurons and circuits may be altered in patients with autistic disorders. Gabaergic and/or connective interneuronal functional abnormalities can represent the anatomical substratum of an imbalance between the activator/inhibitor functions of the perception of sensations, memory, emotions and social relationships, which have been related with the autistic brain. A disorder in the maturing of the gabaergic connections results in structural and functional immaturity of the cerebral cortex, by affecting neuronal migration and differentiation, synaptogenesis and the formation of circuits [41].

Table 1. Tests assessing the effect on the CNS of drugs which affect psychomotor performance

1. Subjective tests. Questionnaires with specific questions on somnolence or lassitude: Stanford sleepiness scale, visual analogue scales and others

2. Objective psychometric tests
   - Sensory-motor coordination tests
     - *Critical tracking test*
     - Visual-motor coordination
     - Total reaction time: Simple + complex
   - Evaluation of cortical functions
     - Processing: Mental calculation tests
     - Integration: Critical flicker fusion or critical fusion frequency
     - Memory: Digit span or numerical tests
     - Learning: List of words
   - Evaluation of sensory functions and state of alertness
     - Detection of stimuli: Auditory vigilance, dynamic visual acuteness
     - Perception: Cancellation, spatial perception, colour test
     - Recognition: Numerical key or Digit symbol substitution
   - Evaluation of motor functions
     - Coordination: Manual dexterity
     - Others: Tapping, body rocking, hand tremor

3. Neurophysiological tests
   - EEC recordings:
     - Continuous EEG monitoring
     - *Multiple Sleep Latency test*
   - Auditive evoked potentials: P-300

4. Simulated driving and piloting tests
5. Real driving tests
   - Standardised driving test in healthy volunteers (Highway Driving Test)
   - Car-Following Test

*CNS: Central Nervous System.

Interactions between antihistamines and benzodiazepines

Various studies have been carried out on the possible inte-ractions between BZD and AH, with special attention being paid to their effects on the CNS. In some cases studies have been done to evaluate the safety of this association and, in other cases, the objective has been different, observing whether their joint administration has a better therapeutic result in pathology related with the anxiety syndrome or insomnia. Table 1 [42] describes the tests normally used to assess the effect on the CNS of drugs which affect psychomotor performance. This work has been done with AH of both first and second generation. Given the different characteristics of both types of drugs, principally with regard to their respective effects on the CNS, it is appropriate to describe them separately.

Interactions between benzodiazepines and first generation antihistamines

In a double blind, placebo controlled study carried out with 44 patients, lasting 4 weeks, in order to compare the therapeutic effect (hypnotic and anxiolytic) resulting from the association of lorazepam 1 mg + diphenhydramine 25 mg in the same medicine, against lorazepam 1 mg alone, for the treatment of insomnia related with the generalised anxiety disorder, it was found objectively, using clinical (scales of symptoms, psychometric tests), psychophysiological (critical frequency of blinking, reaction time, variability in reaction time) and polysomnographic criteria to establish the quality of sleep and waking, with electroencephalograph to measure the cerebral electric activation, that the lorazepam 1 mg + diphenhydramine 25 mg combination was superior in its hypnotic and anxiolytic effects than the administration of lorazepam 1 mg alone [43, 44].

In another double blind, crossed study, carried out with 20 healthy male volunteers, the effects of terfenadine (60, 120 and 240 mg) and diphenhydramine (100 mg) were studied, alone or in combination with diazepam (10 mg) or alcohol (0.75 g/kg), all taken orally, with respect to psychomotor effects and effects on subjective sensations. The result demonstrated that diphenhydramine significantly worsened

Table 2. Central interactions of first generation antihistamines with benzodiazepines

		Subjective tests	Objective psychomotor tests	Neurophysiological tests
Saletu, Grunberger [43, 44]	Lorazepam 1 mg	+	+	+
	Lorazepam 1 mg + Diphenhydramine 25 mg	++	++	++
Moser [45]	Diphenhydramine 100 mg	+	+	ND
	Diphenhydramine 100 mg + Diazepam 10 mg	++	++	ND
	Diphenhydramine 100 mg + Alcohol 0,75 g/kg	++	++	ND
Mattila [46]	Diphenhydramine 50 mg	+	+	ND
	Diazepam 0.3 mg/kg	+	+	ND
	Diphenhydramine 50 mg + Diazepam 0.3 mg/kg	+	+	ND
Saletu, Grunberger [47]	Diphenhydramine 50 mg	+	+	+
	Lorazepam 2 mg	+	+	+
	Diphenhydramine 25 + Lorazepam 1 mg	+	+	+
	Diphenhydramine 50 mg + Lorazepam 2 mg	++	++	++

Abbreviation: ND: Not Done
+: Presents depressant effects on the Central Nervous System (CNS) in the tests done; ++: The association of both drugs increases the depressant effects on the CNS.

the results for psychomotor abilities on being combined with diazepam [45].

Mattila et al. [46] described the acute and sub-acute effects produced in psychomotor performance by the oral administra¬tion of diphenhydramine (50 mg/12 hours), for 5 days, combined with a single oral dose of diazepam of 0.3 mg/kg. Subjective and objective tests were used to measure the effects. In this case no reduction was observed in psychomotor performance with the combination with BZD. The authors explain this situation as secondary to the development of tolerance to the central effects of diphenhydramine after having administered multiple doses.

Saletu et al. and Grünberger et al. [47] studied the effects of oral doses of diphenhydramine 50 mg, lorazepam 2 mg and the combinations of diphenhydramine 25 mg + lorazepam 1 mg and diphenhydramine 50 mg + lorazepam 2 mg, with respect to electroencephalograph recording and psychometric tests. It was observed that the largest effect on the recording and tests was produced by the diphenhydramine 50 mg + lorazepam 2 mg combination and the least effect on the CNS was shown by diphenhydramine alone at a dose of 50 mg. No differences were found between the diphenhydramine 25 mg + lorazepam 1 mg combination and the dose of lorazepam 2 mg.

Table 2 summarises the central interactions of first generation AH with BZD.

Interactions between benzodiazepines and second generation antihistamines

Patat et al. [49] studied the effects on psychomotor performance, cognitive functions and memory in the short and long term produced in 16 healthy young males by the administration of mizolastine 10 mg/day or placebo for 8 days, giving one dose of lorazepam 2 mg or placebo on days 6 and 8. The results showed an absence of effects on the parameters studied with the administration of mizolastine, however the administration on days 6 and 8 of 2 mg lorazepam did alter the psychomotor performance, cognitive functions, induced anterograde amnesia and produced somnolence from 2 to 8 hours after administration of the dose. Mizolastine did not increase the depressant effects on the cerebral functions produced by lorazepam when administered together.

Mattila et al. [50] described the objective (psychophysiological measurements) and subjective (questionnaires, analogue visual scales) effects on the CNS in 12 healthy volunteers after the administration of ebastine 20 mg or placebo for 1 week, associated on the 7th day with a single dose of diazepam 15 mg. Ebastine did not affect the performance of the CNS, however it was affected in all its parameters by the administration of 15 mg diazepam. Joint administration (ebastine + diazepam) did not worsen the results obtained with diazepam alone.

Table 3. Central interactions of second generation antihistamines with benzodiazepines

		Subjective tests	Objective psychomotor tests	Neurophysiological tests
Patat [49]	Mizolastine 10 mg	–	–	ND
	Lorazepam 2 mg	+	+	ND
	Mizolastine 10 mg + Lorazepam 2 mg	+*	+*	ND
Moser [45]	Terfenadine 60, 120, 240 mg	–	–	ND
	Diphenhydramine 100 mg	+	+	ND
	Terfenadine 120 mg + Diazepam 10 mg	+*	+*	ND
	Terfenadine 120 mg + Alcohol 0,75 gr/kg	+*	+*	ND
Mattila [50]	Ebastine 20 mg	–	–	ND
	Diazepam 15 mg	+	+	ND
	Ebastine 20 mg + Diazepam 15 mg	+*	+*	ND
Mattila [46]	Temelastine 100 mg	–	–	ND
	Diazepam 0,3 mg/kg	+	+	ND
	Temelastine 100 mg + Diazepam 15 mg	+*	+*	ND
García Gea [51]	Rupatadine 10 mg	–	–	ND
	Lorazepam 2 mg	+	+	ND
	Rupatadine 10 mg + Lorazepam 2 mg	+*	+*	ND
Bachert C [52]	Bilastine 20 mg	–	–	ND
	Lorazepam 3 mg	+	+	ND
	Bilastine 20 mg + Lorazepam 3 mg	+*	+*	ND

Abbreviation: ND: Not Done
+: Presents depressant effects on the Central Nervous System (CNS) in the tests done; +*: The association of both drugs does not increase the depressant effects on the CNS.

Moser et al. [45] described that terfenadine in doses of up to 120 mg/day does not produce effects on psychomotor performance, or cause more impairment than that produced by 100 mg diphenhydramine when both drugs were administered together.

Mattila et al. [46] observed the absence of alteration in the objective and subjective parameters of cerebral function after the administration of 100 mg/12 hours of temelastine in daily administration for 5 days. The administration together with diazepam 0.3 mg/kg on the 5th day produced alterations in cerebral function, but was not increased by joint administration with temelastine.

García Gea et al. [51] studied the pharmacological behaviour of rupatadine 10 mg/day for 1 week and whether it increased the depressant effects on the CNS produced after giving a single dose of lorazepam 2 mg on days 5 and 7. This was a double blind, randomised study, placebo controlled and crossed, with 16 healthy volunteers. Psychometric tests and visual analogue scales were used for the measurements. The results showed an absence of effect on cerebral function by the rupatadine 10 mg/day, while the administration of 2 mg lorazepam did produce somnolence and altera¬tions in psychomotor performance, which were similar for its administration alone and when combined with rupatadine, so that it is concluded that rupatadine did not increase the depressant effects on the CNS produced by lorazepam.

In another work including 18 healthy volunteers it was assessed whether treatment with bilastine 20 mg/day strengthened the depressant effect of lorazepam 3 mg/day after a single administration and after repeated doses for 8 days. With a double blind design, placebo controlled and crossed, 3 treatments were given: placebo, lorazepam 3 mg or bilastine 20 mg + lorazepam 3 mg. A subjective (questionnaires) and objective (psychomotor performance test) assessment was carried out. The results showed that the combination of bilastine and lorazepam did not induce a

greater deterioration, either subjective or objective, than the deterioration produced by lorazepam alone, either in single dose or in repeated doses (8 days) [52], a circumstance which establishes the safety of bilastine in relation with its effects on the CNS [53]. Table 3 summarises the central interactions of second generation AH with BZD.

Conclusions

First generation AH interact with BZD and increase their sedative effects. This has been used for therapeutic purposes in diseases which associate clinical anxiety or sleep disorders, but in other different circumstances this depressant synergy of the CNS functions must be taken into account before the pharmacology prescription due to the negative consequences which can be produced in a patient.

Second generation AH do not increase the sedative effects of BZD [45, 49, 50], which makes these the drugs of choice for treating allergic rhinitis/rhinoconjunctivitis and urticaria in patients who also receive BZD.

Acknowledgements

JB and MF belong to the Network for Research into Adverse Reactions to Allergens and Drugs (Red de Investigación de Reacciones Adversas a Alérgenos y Fármacos) (RIRAAF) RD12/0013 of the Carlos III Institute.

References

1. Church MK. Safety and efficacy of bilastine: a new H(1)-antihistamine for the treatment of allergic rhinoconjunctivitis and urticaria. Expert Opin Drug Saf. 2011. 10(5): p. 779-93.
2. Simons FE, Simons KJ. Histamine and H_1-antihistamines: celebrating a century of progress. J Allergy Clin Immunol. 2011. 128(6): p. 1139-1150 e4.
3. Kannan P, John C, Zoghbi SS, Halldin C, Gottesman MM, Innis RB, et al. Imaging the function of P-glycoprotein with radiotracers: pharmacokinetics and in vivo applications. Clin Pharmacol The. 2009. 86(4): p. 368-77.
4. Stanley LA, Horsburgh BC, Ross J, Scheer N, Wolf CR, et al. Drug transporters: gatekeepers controlling access of xenobiotics to the cellular interior. Drug Metab Rev. 2009. 41(1): p. 27-65.
5. Cardoso FL, Brites D, Brito MA. Looking at the blood-brain barrier: Molecular anatomy and possible investigation approaches. Brain Res Rev. 2010. 64(2): p. 328-63.
6. Montoro J, Sastre J, Bartra J, del Cuvillo A, Dávila I, Jáuregui I, et al. Effect of H_1 antihistamines upon the central nervous system. J Investig Allergol Clin Immunol. 2006. 16 Suppl 1: p. 24-8.
7. Holgate ST, Canonica GW, Simons FE, Taglialatela M, Tharp M, Timmerman H, et al. Consensus Group on New-Generation Antihistamines (CONGA): present status and recommendations. Clin Exp Allergy. 2003. 33(9): p. 1305-24.
8. Camelo-Nunes IC. New antihistamines: a critical view. J Pediatr (Rio J). 2006. 82(5 Suppl): p. S173-80.
9. Chen C, Hanson E, Watson JW, Lee JS. P-glycoprotein limits the brain penetration of nonsedating but not sedating H_1-antagonists. Drug Metab Dispos. 2003. 31(3): p. 312-8.
10. Vinkers CH, Olivier B. Mechanisms Underlying Tolerance after Long-Term Benzodiazepine Use: A Future for Subtype-Selective $GABA_A$ Receptor Modulators? Adv Pharmacol Sci. 2012. 2012: p. 416864.
11. Becker DE. Pharmacodynamic considerations for moderate and deep sedation. Anesth Prog. 2012. 59(1): p. 28-42.
12. MIhic SJ, HR. Hypnotics and sedatives. Googman and Gilman's The Pharmacological Basis of Therapeutics. 12 th ed. New York, NY. Mc Graw-Hill Companies Inc, 2011.
13. Saari TI, Uusi-Oukari M, Ahonen J, Olkkola KT. Enhancement of GABAergic activity: neuropharmacological effects of benzodiazepines and therapeutic use in anesthesiology. Pharmacol Rev. 2011. 63(1): p. 243-67.
14. Mitchell HA, Weinshenker D. Good night and good luck: norepinephrine in sleep pharmacology. Biochem Pharmacol. 2010. 79(6): p. 801-9.
15. Raber J. Histamine receptor-mediated signaling during development and brain function in adulthood. Cell Mol Life Sci. 2007. 64(6): p. 735-41.
16. Haas H, Panula P. The role of histamine and the tuberomamillary nucleus in the nervous system. Nat Rev Neurosci. 2003. 4(2): p. 121-30.
17. Lin JS, Anaclet C, Sergeeva OA, Haas HL. The waking brain: an update. Cell Mol Life Sci. 2011. 68(15): p. 2499-512.
18. Mochizuki H, Kimura Y, Ishii K, Oda K, Sasaki T, Tashiro M, et al. Quantitative measurement of histamine H(1) receptors in human brains by PET and [11C]doxepin. Nucl Med Biol. 2004. 31(2): p. 165-71.
19. Yoshizawa M, Tashiro M, Fukudo S, Yanai K, Utsumi A, Kano M, et al. Increased brain histamine H_1 receptor binding in patients with anorexia nervosa. Biol Psychiatry. 2009. 65(4): p. 329-35.
20. Tang SC, Arumugam TV, Cutler RG, Jo DG, Magnus T, Chan SL, et al. Neuroprotective actions of a histidine analogue in models of ischemic stroke. J Neurochem, 2007. 101(3): p. 729-36.
21. Orsetti M, Ferretti C, Gamalero R, Ghi P. Histamine H3-receptor blockade in the rat nucleus basalis magnocellularis improves place recognition memory. Psychopharmacology (Berl). 2002. 159(2): p. 133-7.
22. Köhler CA, da Silva WC, Benetti F, Bonini JS. Histaminergic mechanisms for modulation of memory systems. Neural Plast, 2011. 2011: p. 328602.
23. Korotkova TM, Sergeeva OA, Ponomarenko AA, Haas HL. Histamine excites noradrenergic neurons in locus coeruleus in rats. Neuropharmacology, 2005. 49(1): p. 129-34.
24. Brown RE, Sergeeva OA, Eriksson KS, Haas HL. Convergent excitation of dorsal raphe serotonin neurons by multiple arousal systems (orexin/hypocretin, histamine and noradrenaline). J Neurosci, 2002. 22(20): p. 8850-9.
25. Barbara A, Aceves J, Arias-Montano JA. Histamine H_1 receptors in rat dorsal raphe nucleus: pharmacological characterisation and linking to increased neuronal activity. Brain Res. 2002. 954(2): p. 247-55.
26. Kurose Y, Terashima Y. Histamine regulates food intake through modulating noradrenaline release in the para-ventricular nucleus. Brain Res. 1999. 828(1-2): p. 115-8.
27. Bealer SL, Crowley WR. Stimulation of central and systemic

oxytocin release by histamine in the paraventricular hypothalamic nucleus: evidence for an interaction with norepinephrine. Endocrinology. 1999. 140(3): p. 1158-64.
28. Yanovsky Y, Li S, Klyuch BP, Yao Q, Blandina P, Passani MB, et al. L-Dopa activates histaminergic neurons. J Physiol. 2011. 589(Pt 6): p. 1349-66.
29. Tagawa M, Kano M, Okamura N, Higuchi M, Matsuda M, Mizuki Y, et al. Neuroimaging of histamine H_1-receptor occupancy in human brain by positron emission tomography (PET): a comparative study of ebastine, a second-generation antihistamine, and (+)-chlorpheniramine, a classical antihistamine. Br J Clin Pharmacol. 2001. 52(5): p. 501-9.
30. Tashiro M, Kato M, Miyake M, Watanuki S, Funaki Y, Ishikawa Y, et al. Dose dependency of brain histamine H(1) receptor occupancy following oral administration of cetirizine hydrochloride measured using PET with [11C]doxepin. Hum Psychopharmacol. 2009. 24(7): p. 540-8.
31. Tashiro M, Sakurada Y, Iwabuchi K, Mochizuki H, Kato M, Aoki Met al. Central effects of fexofenadine and cetirizine: measurement of psychomotor performance, subjective sleepiness, and brain histamine H_1-receptor occupancy using 11C-doxepin positron emission tomography. J Clin Pharmacol. 2004. 44(8): p. 890-900.
32. Hindmarch I, Shamsi Z, Kimber S. An evaluation of the effects of high-dose fexofenadine on the central nervous system: a double-blind, placebo-controlled study in healthy volunteers. Clin Exp Allergy. 2002. 32(1): p. 133-9.
33. Okamura N, Yanai K, Higuchi M, Sakai J, Iwata R, Ido T et al. Functional neuroimaging of cognition impaired by a classical antihistamine, d-chlorpheniramine. Br J Pharmacol. 2000. 129(1): p. 115-23.
34. Rissman RA, Mobley WC. Implications for treatment: GABAA receptors in aging, Down syndrome and Alzheimer's disease. J Neurochem. 2011. 117(4): p. 613-22.
35. Herrmann R, Heflin SJ, Hammond T, Lee B, Wang J, Gainetdinov RR, et al. Rod vision is controlled by dopamine-dependent sensitization of rod bipolar cells by GABA. Neuron. 2011. 72(1): p. 101-10.
36. Druga R. Neocortical inhibitory system. Folia Biol (Praha). 2009. 55(6): p. 201-17.
37. Gentet LJ. Functional diversity of supragranular GABAergic neurons in the barrel cortex. Front Neural Circuits. 2012. 6: p. 52.
38. Ramamoorthi K, Lin Y. The contribution of GABAergic dysfunction to neurodevelopmental disorders. Trends Mol Med. 2011. 17(8): p. 452-62.
39. Allain AE, Le Corronc H, Delpy A, Cazenave W, Meyrand P, Legendre P, et al. Maturation of the GABAergic transmission in normal and pathologic motoneurons. Neural Plast. 2011. 2011: p. 905624.
40. Hori K, Hoshino M. GABAergic neuron specification in the spinal cord, the cerebellum, and the cochlear nucleus. Neural Plast. 2012. 2012: p. 921732.
41. Sgadò P, Dunleavy M, Genovesi S, Provenzano G, Bozzi Y. The role of GABAergic system in neurodevelopmental disorders: a focus on autism and epilepsy. Int J Physiol Pathophysiol Pharmacol,. 2011. 3(3): p. 223-35.
42. Jáuregui I, Mullol J, Bartra J, del Cuvillo A, Dávila I, Montoro J, et al. H_1 antihistamines: psychomotor performance and driving. J Investig Allergol Clin Immunol. 2006. 16 Suppl 1: p. 37-44.
43. Saletu B, Saletu-Zyhlarz G, Anderer P, Brandstätter N, Frey R, Gruber G, et al. Nonorganic insomnia in generalized anxiety disorder. 2. Comparative studies on sleep, awakening, daytime vigilance and anxiety under lorazepam plus diphenhydramine (Somnium) versus lorazepam alone, utilizing clinical, polysomnographic and EEG mapping methods. Neuropsychobiology. 1997. 36(3): p. 130-52.
44. Grünberger J, Saletu B, Linzmayer L, Böck G, Weissgram S, Brandstaätter N, et al. Comparative studies on the effects of the combination drug lorazepam plus diphenhydramine (Somnium) versus lorazepam on the noopsyche, thymopsyche and psychophysiology in nonorganic insomnia related to generalized anxiety disorder. Methods Find Exp Clin Pharmacol. 1997. 19(9): p. 645-54.
45. Moser L, Hüther KJ, Koch-Weser J, Lundt PV. Effects of terfenadine and diphenhydramine alone or in combination with diazepam or alcohol on psychomotor performance and subjective feelings. Eur J Clin Pharmacol. 1978. 14(6): p. 417-23.
46. Mattila MJ, Mattila M, Konno K. Acute and subacute actions on human performance and interactions with diazepam of temelastine (SK&F93944) and diphenhydramine. Eur J Clin Pharmacol. 1986. 31(3): p. 291-8.
47. Saletu B, Anderer P, Barbanoj MJ. Pharmacodynamic studies of a combination of lorazepam and diphenhydramine and its single components: electroencephalographic brain mapping and safety evaluation. Curr Ther Res. 1988. 44:: p. 909–37.
48. Grünberger J, Linzmayer L, Barbanoj MJ. Pharmacodynamic studies of a combination of lorazepam and diphenhydramine and its single components: psychometric and psychophysiological data. Curr Ther Res. 1988. 44:: p. 938–65.
49. Patat A, Perault MC, Vandel B, Ulliac N, Zieleniuk I, Rosenzweig P. Lack of interaction between a new antihistamine, mizolastine, and lorazepam on psychomotor performance and memory in healthy volunteers. Br J Clin Pharmacol. 1995. 39(1): p. 31-8.
50. Mattila MJ, Aranko K, Kuitunen T. Diazepam effects on the performance of healthy subjects are not enhanced by treatment with the antihistamine ebastine. Br J Clin Pharmacol. 1993. 35(3): p. 272-7.
51. García-Gea C, Ballester MR, Martínez J, Antonijoan RM, Donado E, Izquierdo I,et al. Rupatadine does not potentiate the CNS depressant effects of lorazepam: randomized, double-blind, crossover, repeated dose, placebo-controlled study. Br J Clin Pharmacol. 2010. 69(6): p. 663-74.
52. Bachert C, Zuberbier T. Bilastine in allergic rhinoconjunctivitis and urticaria. Allergy., 2010. 65(Suppl. 93): p. 1-13.
53. Montoro J, Mullol J, Dávila I, Ferrer M, Sastre J, Bartra J, et al. Bilastine and the central nervous system. J Investig Allergol Clin Immunol. 2011. 21 Suppl 3: p. 9-15.

Javier Montoro
Allergy Unit,
Arnau de Vilanova University Hospital,
Faculty of Medicine,
Catholic University of Valencia "San Vicente Mártir"
Valencia

