ORIGINAL

Antihistamines in Drivers, Aircrew and Occupations of Risk

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Resumen

Las enfermedades alérgicas más prevalentes pueden cursar con somnolencia diurna asociada a la propia condición. Los antihistamínicos empleados en su tratamiento pueden tener además efectos centrales y afectar a determinadas ocupaciones de riesgo, la seguridad vial o la navegación marítima y aérea. Las pruebas cognitivas, los estudios experimentales y los datos epidemiológicos aconsejan evitar los antihistamínicos de 1ª generación en conductores habituales y/o profesiones críticas de seguridad. Aunque no hay estudios comparativos en conducción real entre antihistamínicos de 2ª generación, en este tipo de pacientes debería tenderse a prescribir los de menor efecto central posible, especialmente aquellos que sean un buen sustrato de bombas de transporte transmembrana como la glicoproteína P y tengan por tanto baja capacidad de cruzar la barrera hemato-encefálica, permitiendo una ventana terapéutica más amplia. En este sentido, la bilastina es un buen sustrato de glicoproteína P y muestra buena tolerancia a nivel del SNC, tanto a nivel de pruebas psicométricas como en las pruebas protocolizadas de conducción real, aún a dosis dobles de las recomendadas en ficha técnica.

Palabras clave: Antihistamínico. Bilastina. Estudios de conducción real. Glicoproteína P. Pruebas cognitivas. Seguridad vial. Sistema nervioso central.

Abstract

The most commonly occurring allergic diseases can involve a daytime drowsiness associated with the condition itself. The antihistamines used in their treatment can also have central effects and affect certain occupations concerned with risk, road safety and maritime and air navigation. Cognitive tests, experimental studies and epidemiological data recommend avoiding 1st generation antihistamines for people who must drive regularly and/or professions concerned with safety. Although there are no comparative studies on real driving between 1st and 2nd generation antihistamines, in this type of patients there should be a preference for prescribing those with least possible central effect, especially those which are a good substrate for transmembrane transporter pumps such as P-glycoprotein and therefore have a low capacity for crossing the hematoencephalic barrier, thus allowing a broader window for therapy. In this sense, bilastine is a good P-glycoprotein substrate and shows good tolerance at CNS level, in both psychometric trials and real driving test protocols, even at double the dose recommended in the technical file.

Key words: Antihistamine. Bilastine. Real driving studies. P-glycoprotein. Cognitive tests. Road safety. Central nervous system.

Introduction

1.1. Allergy, sleep and antihistamines

Allergy can be a factor of risk in handling vehicles. On the one hand, some very common allergic pathologies can involve daytime somnolence associated with these conditions: allergic rhinitis itself can cause alterations in the quantity and quality of sleep [1-2], and chronic urticaria can produce deleterious effects on all the areas of health-related quality of life, including sleep [3]. That is to say, daytime somnolence can be considered as a problem associated, at least partly, with the allergic pathology itself. On the other hand, the symptoms of allergic rhinitis (bursts of sneezing, difficulties in vision, irritability) can affect the driving of vehicles and, in the case of aviation pilots, can also cause otalgia due to barotrauma, changes in vision and cabin distractions [4].

On the other hand, all the classic antihistamines (AH) and many of the more recent ones can have more or less depressant effects on the CNS (somnolence, lassitude, giddiness, lack of coordination, slowed reaction time), as well as peripheral anticholinergic effects (pupil dilatation, blurred vision or dry mouth), which could affect the control of vehicles and aircraft. Around 15% of the Spanish population receives AH at some point every year, with or without medical prescription, since they are the most frequent form of self-medication in allergic illnesses, the common cold, insomnia and other conditions. The people treated with AH are mostly outpatients and are generally regular drivers. For all these reasons, the use of AH by drivers, especially professionals, aircrew and all those people whose occupations involve critical safety has been a motive for concern and debate for some years [5].

1.2. Antihistamines and road and air accidents

The most recent data on road accidents from the General Directorate of Traffic allows a certain optimism in the balance for the decade: in relation with 2001, the data for the years 2010-2011 show a reduction of more than 55% in deaths and serious injuries from traffic accidents [6]. Many variables may have had an influence in this reduction in morbimortality: safer roads and vehicles, continuous checks on speed and alcohol intake, or a more responsible attitude among drivers. Even so, in Spain there are still around 2,000 deaths and 120,000 people injured on the roads every year, mostly those aged under 40. Among the recurrent factors in accidents with victims, in addition to carelessness, alcohol stands out, together with a series of medicines which are psychotropic or with collateral effects on the CNS (Table 1) [7], present in Spain in up to 6% of drivers killed in traffic accidents [8]. In 1998 the presence of AH was found in 2% of drivers involved in accidents, and in 5% of drivers examined by breathalyser when driving under suspicion of having consumed drugs and alcohol [9].

Again, 1st generation AH were found in samples from pilots in 4-11% of aircraft accidents with victims in the USA between 1990 and 2005; the use of AH, with/without other drugs and/or alcohol, was considered as the principal cause in 13 cases and as a concurrent factor in another 50 out of 338 aviation accidents [10].

Many specialists agree in limiting the free sale of 1st generation AH, alone or included in multiple anti-catarrhal preparations, especially for their involvement in traffic and air or maritime navigation accidents [11]. It is evident that non-sedative AH as a whole are safer from this viewpoint than the classical AH; nevertheless in the study of new AH it has been made essential to assess their effects on psychomotor performance and on driving and piloting, simulated or real.

Table 1. Psychotropic medicines which can affect the driving of vehicles [7]

Opiates (the whole group)
Antipsychotics
Anxiolytics
Hypnotics and tranquillisers
Antidepressants (the whole group) • Non-selective monoamine reuptake inhibitors • Selective serotonin reuptake inhibitors
Drug substitutes in addiction disorders (the whole group) • Bupropion • Methadone • Levacetylmethadol
Antihistamines for systemic use (the whole group) • 1st generation antihistamines • Piperazine derivatives • Other antihistamines for systemic use

2. Psychomotor performance and 2nd generation antihistamines

In studies on the effect of antihistamines and other drugs on psychomotor performance a series of examinations or subjective and objective tests have been used, which are summarised in another article in this supplement.

Apart from their direct action on the CNS and the peripheral anticholinergic effects which can limit the capacity to drive vehicles, AH can present interactions with alcohol, with the mutual enhancement of sedative effects; as well as multiple medicament interactions, most problematical in AH metabolized in the liver through cytochrome p-450 isoenzymes (CYP3A4, CYP2D6).

The sedative effects of AH are associated with their capacity to penetrate the blood-brain barrier (BBB), which depends above all on the lipophilia of the molecule

and its interaction with active transport pumps such as glycoprotein-P (P-gp) or organic anion transporter proteins (OATP), responsible for the outflow or expulsion of xenobiotics from the CNS [12]. Various 2nd generation AH are substrata of P-gp, which has been related with their low penetration in the brain [13-14]; however, other studies suggest large differences between the various molecules in their capacity of crossing the BBB and in the role of P-gp in limiting their transport to the CNS [15].

More than 80 comparative studies (randomised, double blind, placebo controlled, cross-over) using psychometric and/or neurophysiological tests have documented significant differences in psychomotor performance between the 1st and 2nd generation AH, above all in the cognitive processes related with attention and reaction time [16].

In this sense, there are many studies favourable to all the 2nd generation AH of systemic use [17], using various classic AH as active comparators.

The European Union requires medicines marketed in the member countries to be classified in three categories according to their capacity to affect the driving of vehicles (Table 2) [18]. According to the studies referred to above, 1st generation AH are considered in categories II (light-moderate adverse effects) and III (serious or potentially dangerous effects), while 2nd generation AH would come halfway between categories 1 (presumably safe) and II, given the variability of the effects and interactions of the various molecules between some patients and others. For the moment, the only two 2nd generation AH included in category II by the committee of experts are cetirizine and mizolastine [19]. For all the medicines in categories II and III, the Spanish Medicines and Health Products Agency has established the incorporation of a driving pictogram on the label (Figure 1).

Table 2. Classification of medicines according to their capacity to alter the driving of vehicles [18]

Category	Characteristics of the medicine	Blood alcohol contents considered equivalent
I	Presumably safe	<0,2 g/L
II	Produces light or moderate adverse effects	0,2-0,5 g/L
III	Produces serious or potentially dangerous adverse effects	>0,5 g/L

Figure 1. Driving pictogram of the Spanish Medicines and Health Products Agency (AEMPS)

3. Specific cognitive studies with 2nd generation AH

3.1. Cetirizine and levocetirizine

In spite of its affinity with P-gp [14], out of all the 2nd generation AH, cetirizine is the one that has shown the greatest alteration of psychomotor performance at therapeutic doses [20-21], in both cognitive tests and simulated driving [22], and in fact it has been taken as a model of the cognitive deficits associated with histaminergic hypofunction [23]. However, its enantiomer levocetirizine seems to be free of these limitations, even in repeated doses [24-25].

3.2. Loratadine and desloratadine

Loratadine does not alter the performance at therapeutic doses of 10 mg/day, which is evidenced by around twenty studies [26]. However, two studies in aviation using figure/symbol substitution and flight simulators did show an alteration at doses of 20 and 40 mg [27]. Its active metabolite desloratadine does not seem to affect the cognitive tests in any way at therapeutic dose [28], nor does it affect carrying out the manoeuvres essential for pilots [29].

3.3. Rupatadine

It has also been demonstrated in healthy volunteers that this does not affect conventional psychometric tests at therapeutic doses, nor does it have effects added to those caused by small doses of alcohol, in contrast to hydroxyzine and cetirizine [30]. As occurs with loratadine, a large part of its action is through the active metabolite desloratadine, which also seems not to affect cognitive tests at therapeutic doses [28].

3.4. Ebastine

Its molecule crosses the BBB well, due to its lipophilia and/or the fact of inhibiting P-gp [12], while its active metabolite carebastine does not [31], which determines that, in neuroimaging studies, it shows very low occupation of central H1 receptors (<10%) in comparison with chlorpheniramine (>50%) [32]. To remain free of effects on the CNS, it is important that its first-step liver metabolism through cytochrome p-450 (CYP3A4) is not affected by interactions or hepatopathy. The effects of ebastine on healthy volunteers are the same as those of the placebo in all kinds of cognitive tests (except at a repeated dose of 30 mg/day on day 5) [33], as against its active comparators clemastine [34] and triprolidine.

3.5. Fexofenadine

This is a substratum of P-gp and crosses the BBB very poorly [35], so that its therapeutic window is very broad, and even at doses of 360 mg/day (2-3 times the recommended dose) it remains free from effects on the CNS [36]. It has been compared in single dose (120 mg) with cetirizine (20 mg), with significant differences in various psychometric tests, subjective somnolence and occupation of cerebral receptors for neuroimaging [37-38]. On the basis of these grounds, it has come to be considered the AH of choice for aviation pilots and other critical safety activities [39].

3.6. Mizolastine

A review of the 5 studies carried out with mizolastine on healthy volunteers against placebo and against active comparatives of 1st and 2nd generation concluded that mizolastine is free of significant cognitive effects at therapeutic doses, although it affects some functions in doses over 20 mg, including studies on real driving [40].

3.7. Bilastine

The preclinical studies indicate that this is a good substratum of P-gp, which could contribute to its little penetration of the BBB, as was demonstrated by studies of tissue distribution with the marked molecule ([14C]-bilastine) using total body auto-radiography techniques, in which no measurable levels of radioactivity were detected in the brain or spinal medulla of a rat [41].

A randomized study of healthy volunteers compared the effect on the CNS of the administration of 3 different doses of bilastine (20, 40 and 80 mg) for 7 days continuously, using hydroxyzine as the active comparator; only the 80 mg dose caused a discrete impairment in psychomotor tests [42]. Also another study on healthy volunteers demonstrated that only the 80 mg dose of bilastine heightens the effects of alcohol (0.8 g/kg) in a manner comparable to cetirizine 10 mg or hydroxyzine 25 mg, not the therapeutic 20 mg dose [43]; which did not increase the effects of a 3 mg dose of lorazepam, either in sole administration, or in administration throughout 8 consecutive days [44].

4. Experimental studies with antihistamines on real driving

Over 25 years ago, in Maastrich (Netherlands), a standardized test was made on driving in normal traffic [45] and, since then, numerous double blind studies have been carried out against placebo and active comparatives in healthy volunteers. The studies take place with specially prepared vehicles, with dual controls, a camera mounted on the top, infrared distance sensors and a computer. In the vehicle are the subject under study, a supervisor (driving school teacher) and an engineer. The vehicles are able to measure, at all times, the speed, angle of turn of the steering wheel and lateral deviation with respect to the road lines. They are also equipped to monitor ECG, EEG and eye movements. Using these cars, tests can be carried out on deviation on the motorway and also the car-following test.

1. ***Standardized driving test in healthy volunteers (Highway Driving Test).*** Driving the prepared vehicle on a motorway, on a circuit of 100 km (50 km each way) at constant speed (90-95 km/h) and in a stable position in the right lane, with a recording made of the whole trip. The principal parameter measured is the ability to keep the vehicle in the centre of the lane, which is expressed as the standard deviation from the lateral position in cm (SDLP) (Figure 2) [46]. This is calibrated in accordance with previous measurements made in experimental conditions for various legal limits of blood alcohol content, and with respect to placebo (Table 3).
2. ***Car-following Test.*** This experiment evaluates particularly the ability to match the speed (60-70 km) of a vehicle in front (at a fixed distance of 15-30 m) and to respond to its brake lights, in a series of acceleration-deceleration manoeuvres (Brake Reaction Time). The test measures parameters such as the coherence or accuracy of adaptation to the speed, the module or factor of amplification between both signals, and the delay or displacement of one signal with respect to the other [47].

A review of 16 studies carried out with various AH using these standardized driving tests in healthy volunteers in 2004 [46] concluded that:

- 1st generation AH significantly affect driving ability, both after a single dose and after a repeated daily dose.
- 2nd generation AH such as mequitazine, cetirizine, loratadine, ebastine, mizolastine, acrivastine or emedastine can also affect driving ability, but in a very variable way, depending on the dose and the interval between dose and test, and in general with the development of tolerance in 4-5 days. The biggest differences with respect to the placebo were for emedastine [48]. For 2nd generation AH such as fexofenadine, desloratadine or levocetirizine, the results against placebo and alcohol were also optimum in studies on healthy

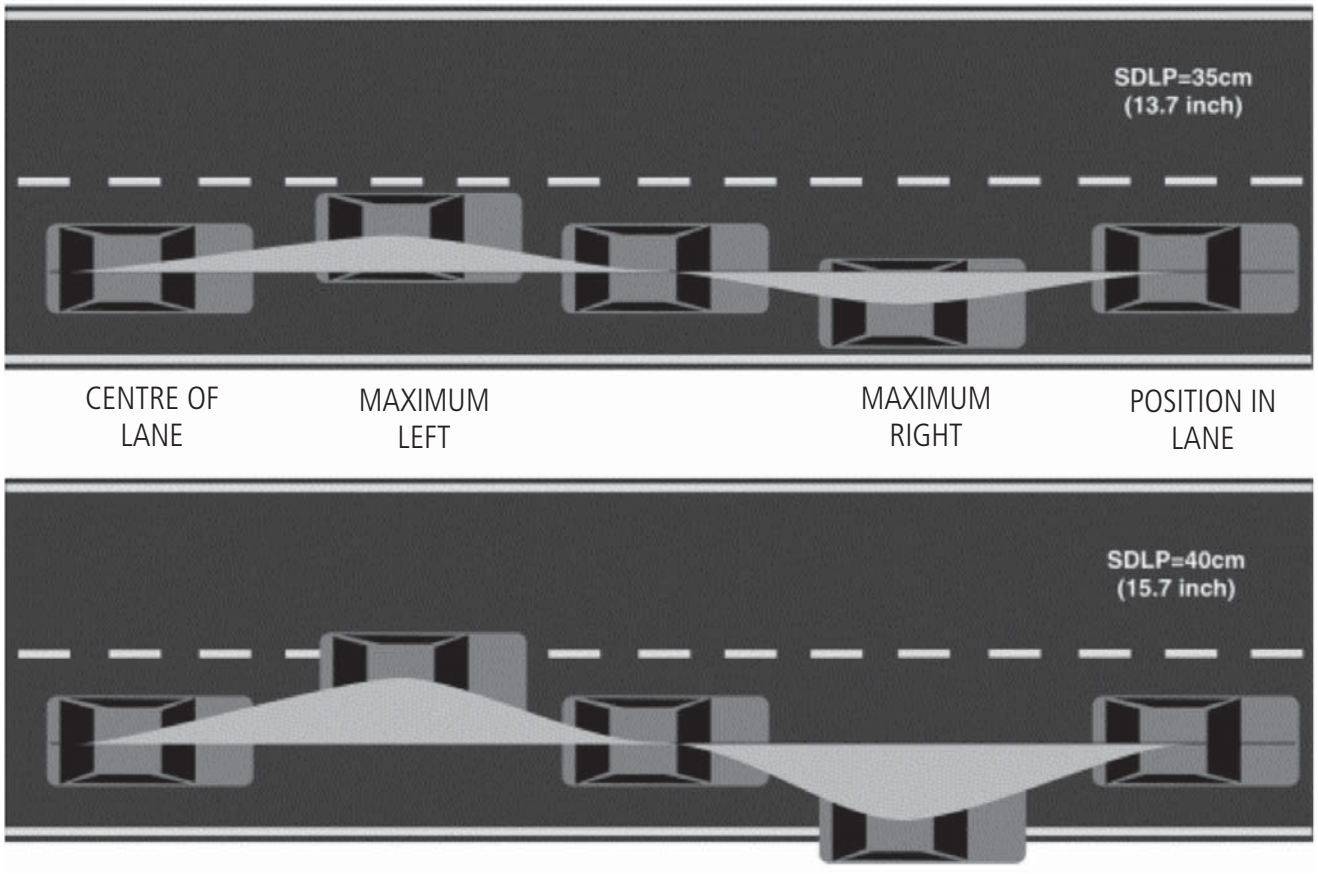


Figure 2. In the standardized highway driving test in healthy volunteers, the principal parameter measured is the ability to keep the vehicle in the centre of the lane, or the standard deviation from the lateral position in cm (SDLP) [46]

Table 3. Legal limits of blood alcohol content and standard deviation from lateral position (SDLP) [46]

Blood Alcohol	SDLP
0.05%	+ 2.6 cm
0.08%	+ 4.1 cm
0.10%	+ 5.3 cm

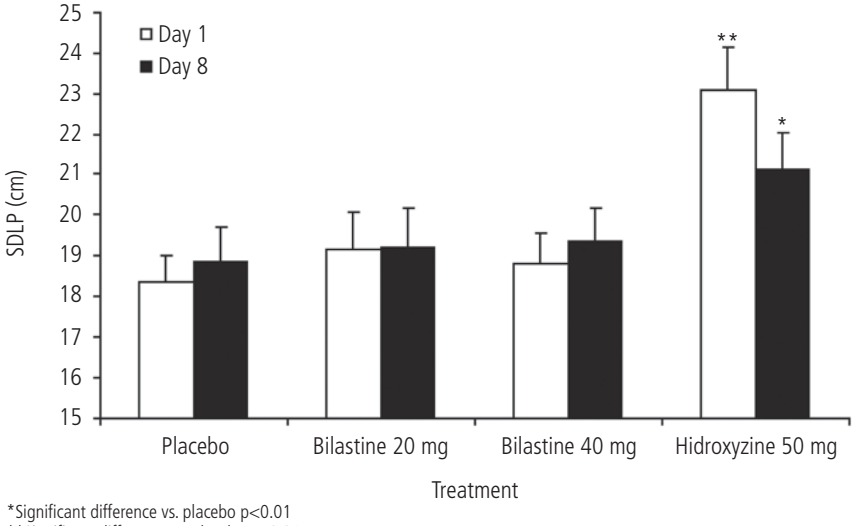
volunteers. Comparative studies (in real driving) between 2nd generation AH are scarce and not conclusive.

- The association of AH with alcohol shows additional effects on the impairment of driving ability, which has been demonstrated for at least some antihistamines, such as cetirizine and loratadine [49].
- In general, the association of 2nd generation AH with pseudoephedrine has not demonstrated a real improvement on psychomotor performance and driving ability with respect to the antihistamine alone [50]. In any case, the possible improvement would come after several days of administration, since the concentration of pseudoephedrine accumulates over time [51].
- At present, there are no studies of real driving which examine the effects of antihistamines with the concomitant use of other medications.

Subsequent to this review, studies have been carried out on real driving with rupatadine [52] and bilastine [53] in healthy volunteers, in both cases against placebo and using hydroxyzine 50 mg as the active comparator, and in both cases using the zigzag or standard deviation from the lateral position in cm (SDLP) as the primary variable, with Brake Reaction Time as secondary variable.

The study with rupatadine [52] was carried out in 20 subjects of both sexes with a single dose of 10 mg, demonstrating similar behaviour between rupatadine 10 mg and placebo, with significant differences in SDLP for hydroxyzine 50 mg against placebo and against rupatadine 10 mg ($p<0.001$ for both comparisons). In the car-following test, the results were not conclusive (not showing any distinction from the placebo for either rupatadine 10 mg or the active comparative).

The primary objective of the study with bilastine [53] was



*Significant difference vs. placebo p<0.01
**Significant difference vs. placebo p<0.01

Figure 3. Typical deviation from lateral position (TDLP or SDLP) for each drug on day 1 and day 8 [53]

to assess the effect of single doses of 20 and 40 mg against placebo and hydroxyzine 50 mg as positive control on the ability to drive vehicles. The secondary objectives were to assess the effects of repeated doses (7 days) of bilastine 20 and 40 mg, and the safety and tolerance of both doses. 20 healthy volunteers of both sexes were selected, distributed in a double-blind cross-over trial in four arms. After both single dose and repeated doses, bilastine 20 mg and 40 mg gave the same results as the placebo, while hydroxyzine 50 mg produced a significant reduction in the ability to drive the vehicle (Figure 3). In a manner concordant with the studies done previously with psychometric tests [42], bilastine showed not to alter complex tasks which require correct coordination and a state of alert, such as driving vehicles, even at doses of double that recommended in the technical file.

5. Limitations of studies on real driving

5.1. Individual variability

The studies are done on healthy volunteers, not on patients, whose conditions in themselves (allergic rhinitis) could be causes of somnolence. On the other hand, in most of the studies inter-individual variations become clear in the effects of the drugs on performance [46].

5.2. Variability according to sex

For reasons which are not clear, in several of the trials on real driving women have turned out to be more sensitive to the sedative effects of some AH (acrivastine, emedastine, cetirizine) [46], while in trials with clemastine, mizolastine, fexofenadine, levocetirizine, rupatadine and bilastine no difference between sexes was able to be shown.

5.3. Variability of the concentration in the blood

The effect of AH on driving ability is dependant on dose but, although the studies are generally made with maximum plasma levels (1-4 hours after intake), in many of the studies with AH on real driving there is no linear relation between the blood concentration and the degree of effect on psychomotor performance [46].

5.4. Prematurely abandoned tests

More than 3% of the studies with drugs in real traffic ended before being completed, generally on decision by the examiner, on observing signs of sleepiness or clumsiness in the subject. The SDLP values in the stopped tests were at times over 35 mm, the cut-off point of safe driving, in 6 out of 10 cases; and in 4 out of 5 cases, the subjects were under the effects of the drug studied [54].

6. Conclusions

AH are very frequently used in habitual drivers, and in many cases can produce a depressant action on the CNS and peripheral neurological effects through cholinergic blockage, which can affect the driving of vehicles and therefore road safety, as well as maritime and aircraft navigation. Cognitive tests and experimental studies on real driving indicate that it is very advisable to avoid 1st generation AH for drivers.

Although there are no comparative studies on real driving between 2nd generation AH, cetirizine and mizolastine are considered as category II (light to moderate adverse effects) with regard to their capacity to affect the driving of vehicles [19]; and in habitual and/or professional drivers it seems more sensible to prescribe 2nd generation AH in category I (presumably safe), where there are all the others. In any event, with most of the AH, a certain tolerance of the central effects is developed after several days of continued use.

In English medical literature, fexofenadine has come to be considered the AH of choice for drivers, aircraft pilots and other activities involving critical safety, through being a good substratum of P-gp and crossing the BBB very poorly, which gives it a broad therapeutic window [39]. In this sense, it must be said that bilastine is also a good substratum of transmembrane transport pumps, which could also influence its good tolerance at CNS level [44], since it only alters the common psychometric tests at doses of 80 mg (four times the therapeutic dose), and shows a behaviour in the real driving test similar to the placebo even at doses double than those recommended in the technical file.

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.

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