FLORE
Repository istituzionale dell'Università degli Studi di Firenze

NO DEVELOPMENT OF TOLERANCE TO ANALGESIA BY REPEATED ADMINISTRATION OF H1 ANTAGONISTS

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

Original Citation:

NO DEVELOPMENT OF TOLERANCE TO ANALGESIA BY REPEATED ADMINISTRATION OF H1 ANTAGONISTS / C. GHELARDINI; N. GALEOTTI; A. BARTOLINI. - In: LIFE SCIENCES. - ISSN 0024-3205. - STAMPA. - 63:(1998), pp. PL317-PL322. [10.1016/S0024-3205(98)00483-4]

Availability:

The webpage https://hdl.handle.net/2158/15883 of the repository was last updated on 2017-10-31T12:23:07Z

Published version:

DOI: 10.1016/S0024-3205(98)00483-4

Terms of use:

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf)

Publisher copyright claim:

La data sopra indicata si riferisce all'ultimo aggiornamento della scheda del Repository FloRe - The above-mentioned date refers to the last update of the record in the Institutional Repository FloRe

(Article begins on next page)

02 May 2026

ELSEVIER

PII S0024-3205(98)00483-4

Life Sciences, Vol. 63, No. 22, pp. PL 317-322, 1998
Copyright© 1998 Elsevier Science Inc.
Printed in the USA. All rights reserved
0024-3205/98 $19.00 + .00

PHARMACOLOGY LETTERS
Accelerated Communication

NO DEVELOPMENT OF TOLERANCE TO ANALGESIA BY REPEATED ADMINISTRATION OF H_1 ANTAGONISTS

Carla Ghelardini, Nicoletta Galeotti and Alessandro Bartolini

Department of Pharmacology, University of Florence, Viale G.B. Morgagni 65, I-50134 Florence, Italy

(Submitted July 9, 1998; accepted August 14, 1998;
received in final form September 21, 1998)

Abstract. The effect produced by repeated administration of the H_1-antihistaminics diphenhydramine, promethazine and pyrilamine on their ability to induce antinociception was evaluated in the mouse hot-plate and abdominal constriction tests. Contrary to morphine, baclofen and oxotremorine, the three H_1 antagonists investigated did not promote the development of tolerance to the analgesic effect after 14 days of repeated treatment. H_1 antagonists could, therefore, represent a promising pharmacological approach to the management of chronic pain.© 1998 Elsevier Science Inc.

Key Words: tolerance, analgesia, H_1-antihistamines, diphenhydramine, pyrilamine, promethazine

Introduction

The H_1-receptor antagonists are among the most widely used medications in the world. Antagonists of histamine H_1 receptors produce, in addition to the well known peripheral effects, various central inhibitory actions (Simons and Simons, 1994). Antihistamines have been shown to be analgesic adjuvants in both animal and human studies. They are widely used as adjuvants in preoperative analgesia as well as in postoperative pain and cancer pain (Sunshine et al., 1987). Clinically, hydroxyzine decreases the amount of narcotic that is necessary, provides sedating, and other antihistaminic effects that are helpful in certain clinical situations. Furthermore, hydroxyzine itself has some analgesic effect (Beaver and Freise, 1976). More recently it has been observed that some other antihistaminics, such as diphenhydramine, pyrilamine and promethazine, are endowed with analgesic properties in both laboratory animals (Rumore and Schlichting, 1985) and humans (Campos and Solis, 1980).

Long-term administration of H_1 antagonists does not lead to autoinduction of epathic metabolism or increase their elimination rate (Simons et al., 1988). In studies lasting 4-12 weeks during which compliance was closely monitored, peripheral H_1 receptor blockade in the skin and efficacy against allergic rhinitis did not decrease markedly (Simons and Simons, 1994). On the other hand, the possibility that some central nervous system effects will develop tolerance to H_1 antagonists over prolonged dosing is controversial (Levander et al., 1991; Goetz et al., 1989).

Corresponding Author: CG, Department of Pharmacology, Viale G.B. Morgani 65, I-50134 Florence, Italy, tel: +39 55 4237432, e-mail: ghelard@server1.pharm.unifi.it

To throw some light onto the induction of tolerance in central effects to H_1 antagonists, we investigated the ability of these compounds to enhance the pain threshold in mice after repeated administration.

Methods and Materials

Animals. Male Swiss albino mice (23-30 g) from Morini (San Polo d'Enza, Italy) breeding farm were used. Fifteen mice were housed per cage. The cages were placed in the experimental room 24 h before the test for acclimatization. The animals were kept at 23±1°C with a 12 h light/dark cycle, light at 7 a.m., with food and water *ad libitum*. All experiments were carried out according to the guidelines of the European Community Council.

Hot plate test. The method adopted was described by O'Callaghan and Holzman (1975). Mice were placed inside a stainless steel container, thermostatically set at 52.5 ± 0.1°C in a precision water-bath from KW Mechanical Workshop, Siena, Italy. Reaction times (s), were measured with a stop-watch before and at regular intervals up to a maximum of 60 min after treatment. The endpoint used was the licking of the fore or hind paws. Those mice scoring below 12 and over 18 s in the pretest were rejected (30%). An arbitrary cut-off time of 45 s was adopted.

Abdominal constriction test. Mice were injected i.p. with a 0.6 % solution of acetic acid (10 ml kg^{-1}), according to Koster et al. (1959). The number of stretching movements was counted for 10 min, starting 5 min after acetic acid injection.

Rota-rod test. The apparatus consisted of a base platform and a rotating rod of 3 cm diameter with a non-slippery surface. The rod was placed at a height of 15 cm from the base. The rod, 30 cm in length, was divided into 5 equal sections by 6 disks. Thus, up to 5 mice were tested simultaneously on the apparatus, with a rod-rotating speed of 16 r.p.m. The integrity of motor coordination was assessed on the basis of the number of falls from the rod in 30 s according to Vaught et al. (1985). The performance time was measured before and 15, 30 and 45 min after treatment.

Drugs. The following drugs were used: (±) baclofen (β-p-chlorophenyl GABA) (Sigma); pyrilamine maleate, promethazine hydrochloride, oxotremorine sesquifumarate (RBI); morphine hydrochloride (USL 10/D Florence, Italy), diphenhydramine hydrochloride (De Angeli). All drugs were dissolved in isotonic (NaCl 0.9 %) saline solution immediately before use. Drug concentrations were prepared in such a way that the necessary dose could be administered in a volume of 10 ml kg^{-1} by subcutaneous (s.c.) and intraperitoneal (i.p.) route.

Statistical analysis. Results are given as the mean ± s.e.m.; analysis of variance (ANOVA), followed by Fisher's PLSD procedure for post-hoc comparison, was used to verify the significance between two means. P values of less than 0.05 were considered significant. Data were analyzed with the StatView for the Macintosh computer program (1992).

Results

The mouse hot-plate and abdominal constriction tests, involving respectively thermal and chemical stimuli were used to evaluate the potential development of tolerance, after repeated treatment, against the analgesia induced by pyrilamine (15 mg kg^{-1} s.c.), promethazine (6 mg kg^{-1} s.c.) and diphenhydramine (20 mg kg^{-1} s.c.). Acute administration (day 1) of the above mentioned compounds produced antinociception that peaked 15 min after injection (Fig. 1). The three H_1 antagonists investigated, injected twice daily for 2 weeks (day 14), did not promote the development of tolerance to the analgesics in the mouse hot-plate test (Fig. 1). In the same experimental conditions, analgesic drugs with different mechanisms of action but endowed with the same efficacy of the three H_1 antagonists investigated, such as morphine (7 mg kg^{-1} s.c.), baclofen (4 mg kg^{-1} s.c.) and oxotremorine (100 μg kg^{-1} s.c.), cause the development of complete tolerance to their analgesic activity (Fig. 1).

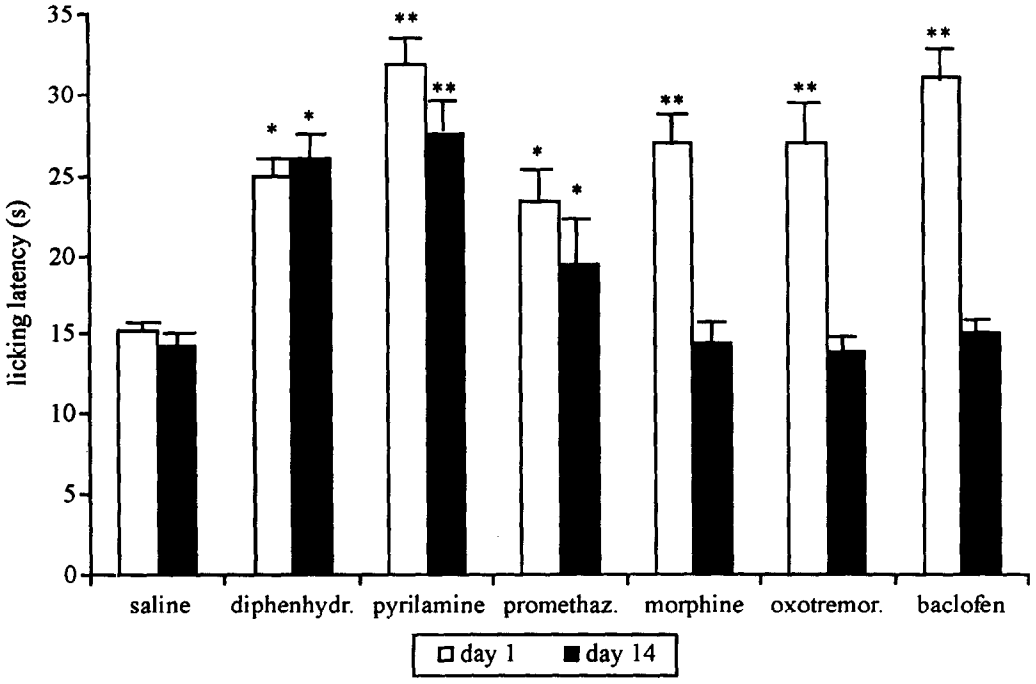

FIG. 1

Effect of repeated administration of pyrilamine, promethazine and diphenhydramine in comparison with morphine, oxotremorine and baclofen in the mouse hot-plate test. Licking latency was recorded in relation to the maximum analgesic effect of each drug. *P<0.01, **P<0.001 versus saline-treated mice

Diphenhydramine (20 mg kg^{-1} s.c.), pyrilamine (15 mg kg^{-1} s.c.) and promethazine (6 mg kg^{-1} s.c.) were able to enhance the pain threshold also in the mouse abdominal constriction test (Fig. 2). Similarly to results with the mouse hot-plate test, the three H_1 antagonists investigated did not cause tolerance to their analgesic activity. Instead, a reduction in the number of abdominal constrictions after repeated administration (day 14) equalled that produced after acute treatment (day 1) (Fig. 2). Similarly to the hot-plate test, in the abdominal constriction test morphine (1 mg kg^{-1} s.c.), baclofen (2 mg kg^{-1} s.c.) and oxotremorine (100 μg kg^{-1} s.c.) cause the development of complete tolerance to their analgesic activity (data not shown).

The analgesic compounds used as reference drugs have been administered at doses, chosen by means of dose-response data, which are analgesically active to antihistamines. Doses of antihistamines used are the highest effective which do not produce behavioral side effects (data not shown).

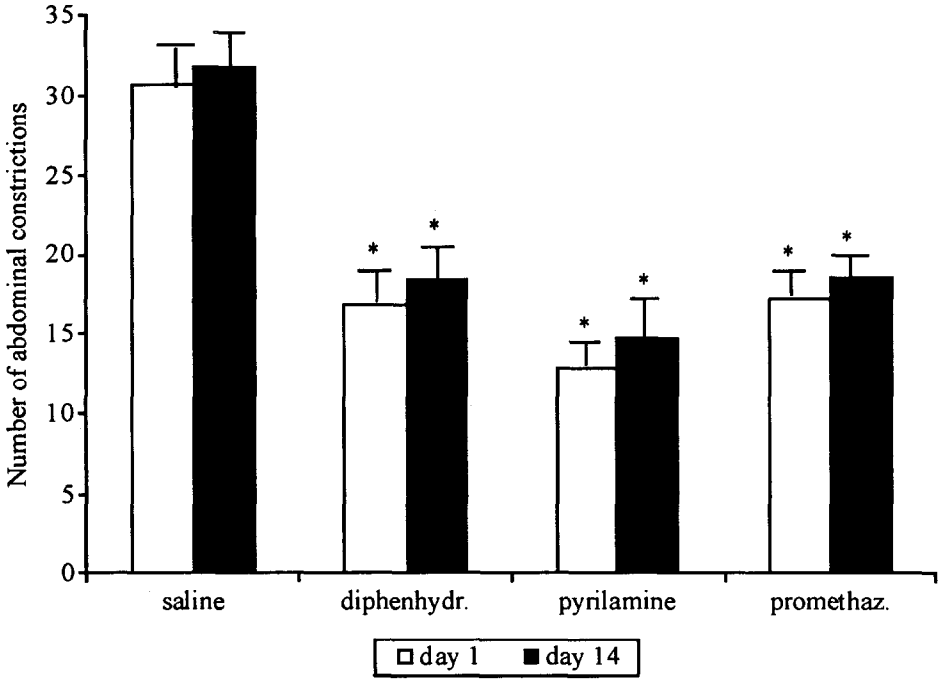

FIG. 2

Lack of development of tolerance to diphenhydramine, pyrilamine and promethazine in the mouse abdominal constriction test. All drugs were injected 15 min before the test. *P<0.001 in comparison with saline-treated mice.

The analgesic drugs investigated, at the doses used, did not modify animals' gross behavior. Moreover, repeated treatment with these compounds did not impair mouse motor coordination as revealed by the rota-rod test (Table 1). By contrast, repeated administration of morphine, baclofen and oxotremorine altered animal's gross behavior and impaired motor coordination as evidenced by an increase of the number of falls of mice from the rotating rod, in comparison with saline-treated mice, in the rota-rod test (data not shown).

TABLE1.

Lack of effect of repeated administration to mice of pyrilamine, promethazine and diphenhydramine on the rota-rod test.

TREATMENT	NUMBER OF FALLS IN 30 S			
mg kg^{-1} s.c.	*pretest*	*15 min*	*30 min*	*45 min*
SALINE	3.7 ± 0.4	2.2 ± 0.4	1.2 ± 0.2	0.9 ± 0.2
PYRILAMINE 15	4.0 ± 0.3	2.7 ± 0.4	1.5± 0.3	0.7 ± 0.2
PROMETHAZINE 6	3.8 ± 0.4	2.3 ± 0.4	1.6 ± 0.3	1.0 ± 0.2
DIPHENHYDRAMINE 20	3.5 ± 0.5	2.1 ± 0.3	1.4 ± 0.2	1.1 ± 0..3

Discussion

Chronic pain is one of the most difficult and perplexing patient problems encountered by physicians. This disorder usually has a disabling effect on the patient's emotional well being, social interaction, work productivity, etc. Many analgesic drugs, such as opiods, NSAID, tricyclic antidepressants, are widely used in the management of chronic pain. However, the major problem with all these drugs is represented by the loss of analgesic efficacy because of the induction of tolerance (Payne et al., 1986).

The development of tolerance with repeated use is a characteristic feature of all the opioid drugs. Tolerance is a physiological response seen in all patients. In particular, spinal opioid use for chronic pain has caused major clinical problems since the high concentrations of opioid in the cerebrospinal fluid create receptor tolerance, especially if those concentrations exceed the level required to alleviate pain (Twycross and McQuay, 1990).

Twice daily administrations for 2 weeks of H_1-antihistaminics to mice did not cause development of tolerance to their analgesic effect representing the first observation of persistent antinociception in animals. In contrast, in accordance with results obtained in humans, subacute treatment for 2 weeks completely abolished analgesia induced by morphine. Moreover, the animals' sensitivity to the antinociception induced by baclofen and oxotremorine was

completely lost following subacute treatment. These data indicate that the experimental schedule used represents an appropriate animal model to unmask the ability to induce tolerance by long-term treatment with analgesic drugs. Therefore, the lack of tolerance observed with the antihistaminics cannot be imputable to an inadequate experimental paradigm, but represents a characteristic feature of this category of drugs. This property of the H_1-antihistaminics is supported by the fact that repeated administration of hydroxyzine did not cause tolerance to sedation, which is another central effect produced by H_1-antihistaminics (Goetz et al., 1989). Nor did, H_1-antihistaminics cause tolerance by peripheral effects to develop. Wheal-and-flare suppression in the skin test reactivity to histamine or allergen, as well as efficacy in ragweed pollen-induced rhinoconjunctivitis, were not suppressed by long-term loratadine and terfenedine treatment (Bousquet et al. 1990; Simons et al., 1988; Juniper et al., 1988).

Repeated administration of H_1-antihistaminics did not alter animals' gross behavior. By day 14 animals' motor coordination was unmodified, as shown by the rota-rod test, indicating beyond doubt that the increase in licking latency, as well as the reduction in abdominal constrictions observed were not due to the animal's altered viability.

Considering that the major drawback of long-term treatment with analgesic drugs consists of the development of tolerance, H_1 antagonists could represent a promising pharmacological approach to the management of chronic pain.

References

1. F.E.R. SIMONS AND K.J. SIMONS, N. Engl. J. Med. 330 1663-70 (1994).
2. A. SUNSHINE, I. ZIGHELBOIM, J.V. SORRENTINO AND R.D. BARTIZEK, J. Clin. Pharmacol. 27 709 (1987)
3. W.J. BEAVER AND G. FREISE, Adv. In Pain Res. Therapy 1 553-557 (1976)
4. M. RUMORE AND D.A. SCHLICHTING, Life Sci. 36 403-6 (1985).
5. V.M. CAMPOS AND E.L. SOLIS, J. Clin. Pharmacol. 20 42-9 (1980).
6. F.E.R. SIMONS, W.T.A. WATSON AND K.J. SIMONS, J. Allergy Clin. Immunol. 82 1068-1075 (1988)
7. S. LEVANDER, M. STAHLE-BACKDAHL AND O. HAGEMARK, Eur. J. Clin. Pharmacol. 41 435-49 (1991)
8. D.W. GOETZ, J , J.M. JACOBSON., J.E. MURNAME, M.J. REID, D.W. REPPERGER, C. GOODYEAR, M.E. MARTIN, J. Allergy Clin. Immunol. 84 316-322 (1989).
9. J.P. O'CALLAGHAN AND S.G. HOLTZMAN J. Pharmacol. Exp. Ther. 197 533-544 (1975)
10. R. KOSTER, M. ANDERSEN AND E.J. DeBEER, Fed. Proc. 18 412 (1959)
11. J. VAUGHT, K. PELLEY, L.G. COSTA, P. SETHER AND S.J. ENNA Neuropharmacol. 24 211-216 (1985).
12. B. PAYNE AND M.A. NORFLEET, Pain 26 1-22 (1986).
13. R.G. TWYCROSS AND H.F. McQUAY, *Textbook of Pain*, P.D. Wall and R. Melzack (Eds), 686-701, Churchill Livingstone, New York (1990).
14. J. BOUSQUET, I. CHANAL, W. SKASSA-BROCIEK, C. LEMONIER AND F.B. MICHEL, J. Allergy Clin. Immunol. 86 248-253 (1990).
15. E.F. JUNIPER, J. WHITE AND J. DOLOVICH, J. Allergy Clin. Immunol. 82 670-675 (1988).