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Effectiveness of repeated administration of a new oral naltrexone controlled-release system on morphine analgesia

J. Álvarez-Fuentes, M. O. Rojas-Corrales, M. A. Holgado, C. Sánchez-Lafuente, J. A. Micó and M. Fernández-Arévalo

Abstract

Naltrexone hydrochloride, an opioid antagonist used as an adjunct to the maintenance of the opioid-free state for detoxified individuals, was introduced into the polymeric structure of Eudragit L30D, an anionic copolymer based on polymethacrylic acid and ethylacrylate. From the results of a preclinical study, this complexation technique can be considered as a useful tool in the design of oral controlled-release systems (naltrexone–Eudragit L) capable of inducing long-lasting effects in-vivo. The biopharmaceutical characterization of the naltrexone–Eudragit L complex in comparison with naltrexone hydrochloride using the mouse hot-plate model has been previously carried out. The results showed a longer effect, an enhancement of 23.47 % of the area under the curve of the inhibition of analgesic activity vs time, and a delay of 51.80 % in the $t_{\frac{1}{2}}$ value induced by the complex, compared with those induced by conventional naltrexone. In this study, a regimen of chronic administration of naltrexone–Eudragit L was established. Thus, in an 8-day treatment (4 doses in alternate days) this oral controlled-release system effectively antagonized the analgesic effect of morphine for 8 h, whereas naltrexone hydrochloride has to be administered over 16 days (8 doses in alternate days) to induce the same effect. In the 16-day schedule the complex-induced antagonism lasted over 14 h after administration.

Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Seville, Spain

J. Álvarez-Fuentes, M. A. Holgado, C. Sánchez-Lafuente, M. Fernández-Arévalo

Department of Neuroscience, Faculty of Medicine, University of Cádiz, Spain

M. O. Rojas-Corrales, J. A. Micó

Correspondence: J. Álvarez Fuentes, Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, C/ Professor García González s/n, 41012 Sevilla, Spain. E-mail: arevalo@fafar.us.es

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Introduction

One of the primary goals in research into drug abuse is the development of medications for treatment of opioid abuse and dependence. Naltrexone, a long-acting, orally effective, opioid antagonist, which blocks opioid effects as well as the development of physical dependence, would appear to be ideally suited to the treatment of addiction. An optimal dosage regimen is critical for the treatment and patient compliance in ambulatory opiate detoxification programs. Once the patients have been detoxified and are opiate-free, an opioid antagonist is usually used as an adjunct to the maintenance of the opioid-free state (Crabtree 1984). Under naltrexone treatment, the probability of relapse decreases rapidly, as the opiate agonist produces few or no effects. Although methadone, in decreasing doses, is still widely used for detoxification procedures, rapid and ultrarapid protocols, including opiate receptors antagonists (i.e. naltrexone) have been proposed. Gerra et al (2000) suggest that the use of naltrexone during detoxification facilitated extended naltrexone acceptance and improved the recovery outcome in outpatients. Stable plasma levels are needed to block the effects of agonists if resumption of opiate use

occurs, and a comfortable dosage regimen is critical for the extended treatment in outpatients. An oral controlled-release system of naltrexone that would allow once-a-day administration may account for this purpose as well as providing stable plasma levels.

Naltrexone hydrochloride is absorbed rapidly and almost completely after oral administration, but undergoes extensive first-pass metabolism in the liver. Only 5–20% of an orally administered dose reaches the systemic circulation unchanged. However, its principal metabolite, 6β-naltrexol, is also a pure antagonist and may contribute to the opioid receptor blockade. Mean elimination half-lives for naltrexone and 6β-naltrexol are 3.9 and 12.9 h, respectively (Swinyard 1990).

A naltrexone–Eudragit L complex has been obtained by a complexation technique successfully used with other drugs, such as morphine and carteolol (Álvarez-Fuentes et al 1994a, b; Holgado et al 1995). This controlled-release system has been shown to induce long-lasting effects in-vivo when administered acutely (Álvarez-Fuentes et al 2000). The ability of this complex to induce effective and long-lasting antagonism of opiate effects appears to be a useful tool to treat opiate addiction.

In this study, we investigated the duration of the effect of a naltrexone–Eudragit L complex in-vivo after chronic administration, to establish a pattern of administration closer to clinical practice. As the main goal of the study was to evaluate the effect of the naltrexone complex on morphine effects, analgesia was chosen as a measurable parameter of opiate activity. The hot-plate model in mouse was used, which allowed us to determine the duration of the morphine-blocking effect of this new product when administered chronically. This model was already used to test the activity of the complex in acute administration (Álvarez-Fuentes et al 2000). Moreover, the hot-plate test is usually used as a method for studying opiate antagonists, using morphine (positive control) as a model analgesic (Heilman et al 1976; Carrara et al 1990; Rosland & Hole 1990; Fuentes et al 1994).

Materials and Methods

Drugs

Naltrexone hydrochloride was provided by Zambón S. A. (Barcelona, Spain). Eudragit L30D was obtained from Hüls Española S.A. (Barcelona, Spain), sodium chloride and sodium hydroxide were provided by Panreac (Barcelona, Spain). Morphine hydrochloride was obtained from Alcaliber, S.A. (Madrid, Spain) and sodium carboxymethylcellulose was from Analema (Vizcaya, Spain).

Dosages of morphine and naltrexone are expressed as the salt form. Morphine (10 mg kg^{-1}) was diluted in 0.9% NaCl and injected subcutaneously. Naltrexone hydrochloride (10 mg kg^{-1}) and naltrexone–Eudragit L complex (10 mg kg^{-1} expressed as naltrexone) were dispersed in carboxymethylcellulose (1%, w/v) and administered orally by means of a flexible cannula. All the drugs were administered in a volume of 10 mL kg^{-1}.

Animals

Experiments were carried out using albino male OF1 mice, 25–30 g, (Central Animal Service of University of Cádiz). The mice were maintained in the laboratory under controlled experimental conditions (temperature 21 ± 1°C, relative humidity 55 ± 10%, 12-h light–dark cycle). Free access to food (rodent pellets; Panlab, Barcelona, Spain) and water was allowed until 1 h before the drug administration. The animals were randomly assigned to groups of 10. These groups were housed in Plexiglas cages ($25 \times 50 \times 15$ cm^3) and placed in the test room the day before testing to adapt to the testing environment.

The experimental protocol was approved by the Ethical Committee for Experiments on Animals of the Faculty of Medicine, University of Cádiz (licence no. 079604) and carried out according to the ethical standards of the International Association for the Study of Pain (1980).

Nociceptive test

Mice were placed on a hot plate (Socrel DS37) thermostatically maintained at 55.0 ± 0.2°C (Woolfe and MacDonald 1944). A plastic cylinder was used to confine the mouse to the heat surface of the hot plate. The time elapsed until the first response of the animal (either forepaw or hindpaw licking or jumping) was measured as the pain latency. To avoid tissue injury, animals not responding within 45 s (cut-off time) were removed from the hot plate and a maximal analgesic effect was recorded.

Experimental procedure

The duration of action of either antagonist was determined by their ability to reverse the analgesic effect of 10 mg kg^{-1} morphine (MP), administered 10 min before the test. The antagonistic activity of the naltrexone–

Eudragit L complex on morphine-induced thermal antinociception, compared with that as a result of conventional naltrexone, was evaluated after administration of several doses (1, 4 or 8 doses given on alternate days). For every schedule of administration, several experiments were carried out in parallel. Each experiment tested the groups at a specific time (2, 8 and 14 h after administration) and these groups were not used again thereafter. Two control groups were used: a blank group (S/S) received saline solution, orally and subcutaneously, and an S/MP group received subcutaneous morphine and oral saline solution. The experimental group (SLCN/MP) received naltrexone–Eudragit L (SLCN; 10 mg kg^{-1}, expressed as naltrexone) and morphine. The Naltr/MP group, received naltrexone hydrochloride (Naltr, 10 mg kg^{-1}) and morphine.

Statistical analyses

The latency induced by the S/MP group was considered to be a 100 % antinociceptive effect. Data are expressed as percentages of the response of the S/MP group. Statistical analyses were performed on raw data. The differences between groups were analysed using the Student-Newman-Keuls test following significant main effects of treatment by analysis of variance. Statistical significance was accepted at a value of $P < 0.05$.

Results

Administration of morphine (S/MP) induced an effective and reproducible antinociceptive effect compared with the saline group (data not shown). Table 1 shows

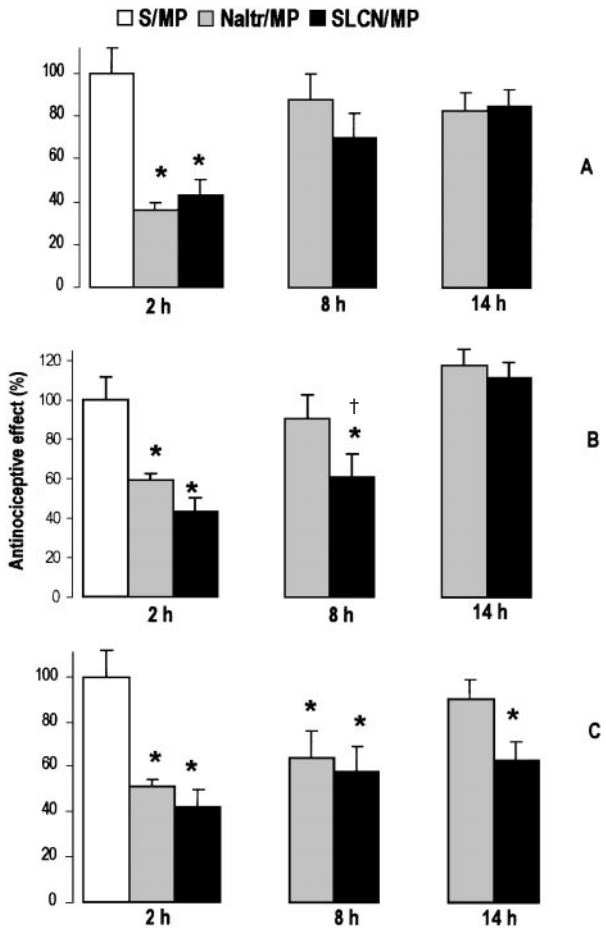

Figure 1 Effect of naltrexone–Eudragit L complex (SLCN) and naltrexone hydrochloride (Naltr) on the antinociceptive effect of morphine hydrochloride (MP) after a single dose (A), after 4 repeated doses (B), and after 8 repeated doses (C). *$P < 0.05$ vs S/MP, †$P < 0.05$ vs Naltr/MP.

Table 1 Parameters obtained from the statistical analyses (Naltr, naltrexone hydrochloride; MP, morphine hydrochloride; SLCN, naltrexone–Eudragit L complex).

Analysis of variance				Post-hoc		
Dose	Test	$F_{(3,36)}$	P	Naltr/MP vs S/MP	SLCN/MP vs S/MP	SLCN/MP vs Naltr/MP
1	2 h	16.2530	$P < 0.01$	$P < 0.05$	$P < 0.05$	–
	8 h	6.9120	$P < 0.01$	–	–	–
	14 h	8.2681	$P < 0.01$	–	–	–
4	2 h	13.5576	$P < 0.01$	$P < 0.05$	$P < 0.05$	–
	8 h	8.0575	$P < 0.01$	–	$P < 0.05$	$P < 0.05$
	14 h	28.3427	$P < 0.01$	–	–	–
8	2 h	10.8376	$P < 0.01$	$P < 0.05$	$P < 0.05$	–
	8 h	5.0175	$P < 0.01$	$P < 0.05$	$P < 0.05$	–
	14 h	3.6947	$P < 0.05$	–	$P < 0.05$	–

data from the statistical analysis of the experiments performed. The antagonistic activity of naltrexone–Eudragit L and naltrexone hydrochloride was evaluated at 2, 8 and 14 h. The following results show the influence of the different patterns of administration on the blockade of morphine-induced antinociception by the naltrexone–Eudragit L complex at the different times of testing. In the first stage, after single administration, naltrexone hydrochloride and the naltrexone–Eudragit L complex significantly antagonized the morphine-induced antinociceptive effect 2 h after administration ($P < 0.05$ Naltr/MP vs S/MP; and $P < 0.05$ SLCN/MP vs S/MP) (Figure 1A). No significant antagonist activity was found in any group at 8 or 14 h after administration. In the second stage, after 4 repeated doses of naltrexone–Eudragit L, administered on alternate days, the antagonist activity was maintained until 8 h after its administration ($P < 0.05$ SLCN/MP vs S/MP) (Figure 1B). Naltrexone hydrochloride did not significantly antagonize the morphine-induced antinociception at this time ($P > 0.05$, Naltr/MP vs S/MP). Furthermore, significant differences were found on the antagonistic activity of naltrexone–Eudragit L and naltrexone hydrochloride at this time-point, 8 h after administration ($P < 0.05$, SLCN/MP vs Naltr/MP). Finally, after 8 repeated doses of the naltrexone complex, administered on alternate days, a significant antagonism of the morphine-induced antinociception was observed (Figure 1C). This antagonism was effective from 2 to 14 h after administration ($P < 0.05$, SLCN/MP vs S/MP). No significant antagonism was found in the Naltr/MP group at the 14 h time-point ($P > 0.05$, Naltr/MP vs S/MP).

Discussion

This investigation was carried out to evaluate the antagonist effect of a naltrexone–Eudragit L complex after repeated oral administration. The naltrexone–Eudragit L complex was elaborated following a technique developed in our laboratory, which has been shown to be effective with other drugs (Álvarez-Fuentes et al 1994a, b; Holgado et al 1995). The in-vitro behaviour of the naltrexone complex has been characterized previously. ^{1}H NMR and ^{13}C NMR spectroscopic studies suggested that naltrexone was present in the polymer as free base and not in its ammonium salt form. So, naltrexone interacts with the polar groups of the polymer, probably, by means of hydrogen bonds. Furthermore, the influence of the pH on the dissolution profiles has been studied (Álvarez-Fuentes et al 1997a).

The activity of the complex was previously studied in-vivo in a regimen of acute administration (Álvarez-Fuentes et al 2000). The study demonstrated that naltrexone–Eudragit L displayed more effective antagonism of the analgesic action induced by subcutaneous administration of morphine than did naltrexone hydrochloride. Effectiveness was measured in terms of duration of blocking action, as a blocking effect is that pursued in the clinical situation. Those results showed that naltrexone hydrochloride significantly blocked the analgesic effect of morphine from 30 min to 10 h after its administration, whereas the antagonism of naltrexone–Eudragit L lasted up to 12 h after treatment. Moreover, at the 10-h time-point, significant differences were found between the antagonism induced by naltrexone–Eudragit L and that induced by naltrexone hydrochloride. Any effect of the polymer Eudragit L on the pain latency was also discounted by previous studies (Álvarez-Fuentes et al 1997b).

When chronic treatment was established, naltrexone–Eudragit L induced an effective antagonism of the morphine-induced analgesic effect in the 16-day schedule, over 14 h after administration. In the 8-day treatment (4 doses on alternate days) the antagonism was effective over 8 h after the last dose, whereas naltrexone hydrochloride had to be administered over 16 days (8 doses on alternate days) to induce the same lasting effect.

These results are in accord with those obtained from the study of acute administration: considering the plot of the inhibition of analgesic activity vs time, naltrexone–Eudragit L provided a delay of 51.80% in the $t_{\frac{1}{2}}$ parameter, compared with that induced by naltrexone hydrochloride.

The testing times were selected based on previous results from acute administration. The first testing time was chosen at 2 h after treatment, as an effective antagonism was demonstrated at this time. The second testing time was chosen at a time-point in which the antagonism began to decrease in one of the groups treated acutely; this was 8 h after treatment. Finally, 14 h after one dose, no antagonism was found in acute experiments.

Naltrexone–Eudragit L showed a longer lasting effect than conventional naltrexone after chronic treatment in the hot-plate test model in mice. These results suggest the usefulness of the proposed complexation technique with Eudragit L30D as a tool in the design of oral controlled-release systems capable of inducing long-lasting effects in-vivo. The complexes obtained can be formulated in several different dosage forms, such as suspensions, capsules, tablets and inert matrices, thereby

allowing for the design of the optimal dosage form. The results are an advance in the development of controlled-release systems for naltrexone. The complexation technique used appears to be effective in providing controlled-release systems. In adequate formulations these controlled-release systems may account for treatment compliance, as well as for providing stable plasma concentrations.

Conclusions

In this study, the in-vivo effect on morphine analgesia of a naltrexone–Eudragit L complex, after a regimen of chronic administration, was demonstrated in comparison with naltrexone hydrochloride. Under our conditions, this oral controlled-release system in an 8-day treatment effectively antagonized the analgesic effect of morphine for 8 h, whereas naltrexone hydrochloride had to be administered over 16 days to induce the same effect. Furthermore, in the 16-day schedule, the complex-induced antagonism lasted over 14 h after administration. These results can be related to those obtained in the study of acute administration (Álvarez-Fuentes et al 2000); considering the plot of the inhibition of analgesic activity (%) vs time, naltrexone–Eudragit L complex provided an enhancement of 23.47% of the area under the curve and a delay of 51.80% in the $t_{\frac{1}{2}}$ parameter, compared with that induced by naltrexone hydrochloride under the same conditions. Thus, the use of this oral naltrexone complex to treat opiate addiction by inducing effective and long-lasting antagonism of opiate effects has been demonstrated.

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