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A Spirohydantoin Derivative of Oxymorphone: An Agonist With Delayed Antagonist Activity

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ALEXANDER, G. J., N. CHATTERJIE AND H. M. WISNIEWSKI. *A spirohydantoin derivative of oxymorphone: An agonist with delayed antagonist activity*. PHARMACOL BIOCHEM BEHAV **32**(4) 939–943, 1989.—We have synthesized a novel derivative of oxymorphone, oxymorphone-6α-spirohydantoin. The derivative was less toxic in mice than the parent compound and it showed a significant anticonvulsive activity. It exerted agonist effects in doses lower than those of morphine and its agonist effects were longer lasting. Furthermore, both oxymorphone and the 6-spirohydantoin showed definite antagonist properties 48 hr later: they prevented analgesic effects of morphine. The antagonist effects of the derivative persisted for a week.

Agonist activity Analgesia Antagonist activity Morphine Opiates Oxymorphone Pain thresholds Oxymorphone-6-spirohydantoin

WE have previously reported that addition of a hydantoin moiety at carbon-6 of the opioid molecule does not significantly alter the initial agonist or antagonist properties of the parent compounds (2, 5, 6). Others have shown that affinity for morphine binding sites in the brain remains largely unaffected by substitutions at the carbon-6 position (3, 13, 14, 16). However, we have considered the possibility that addition of a large polar group might lead to an increase in overall polarity of the molecule and to slower penetration through biological membranes. The latter would result in a decrease in peak concentrations and, thereby, in overall toxicity but prolongation of the duration of action (8). In addition, presence of the added polar group might cause irreversible binding of the new compounds in vivo with concomitantly longer-lasting effects and perhaps different mechanisms of development of tolerance. The possibility of multiple binding and multiple effects, occasionally even opposite effects (i.e., agonist/antagonist), at the various sites was also raised (9).

When we tested the effects of new spirohydantoin derivatives of oxymorphone as well as oxycodone, naloxone and naltrexone in vivo in mice within 30 min of an IP injection of 1 mg/kg, we found that the first two acted as potent and rapid agonists, largely comparable in action to morphine, and the latter two either did not affect pain thresholds or may have decreased them slightly, making the animals more aware of pain (2). When morphine was administered along with or 30 min after treatment with naloxyl- or naltrexyl-6-spirohydantoin, it was found ineffective. The antagonist effects of naloxyl- and naltrexyl-6-spirohydantoins were still observed at 48 and 72 hr after treatment and waned after a week (8). Injection of morphine sulfate (5 mg/kg) exerted no effect on pain thresholds in mice pretreated 48–72 hr earlier with either spirohydantoin antagonist. Surprisingly, however, derivatives of oxymorphone and oxycodone also antagonized morphine 48 hr after their injection. Thus, the latter two compounds showed mixed agonist/antagonist effect: agonist in 30 min and antagonist in 48 hr. Preliminary notes describing these findings have been published (2,8). In this paper we compare the agonist/antagonist effects of oxymorphone with those of its newly-synthesized 6-spirohydantoin derivative.

METHOD

Chemicals

The starting material, oxymorphone hydrochloride, was kindly provided by the Mallinckrodt Corporation, St. Louis, MO. Other chemicals were purchased from Endo Labs, Garden City, NY, Knoll Pharmaceutical Company, Nutley, NJ, Fisher Scientific Corp., Orange, NJ and Sigma Chemical Corp., St. Louis, MO.

We synthesized the oxymorphone-6α-spirohydantoin by reacting oxymorphone, potassium cyanide and ammonium carbonate in acetamide in a pressure bottle at 100–110°C for several hours. The reaction mixture was then digested with HCl at pH 2–3, made alkaline with NaOH to pH 9 and extracted with solvents. The product, dried over sodium sulfate, was recrystallized from aqueous ethanol as a white monohydrate, m.p. 340°C. It was converted to water-soluble hydrochloride for biological testing. Details of the synthesis and structure assignment will be published elsewhere.

Animals

Albino mice, male, 25 ± 5 g, were purchased from the Charles River Labs, Wilmington, MA. A total of 240 animals, in groups of 10, were used in this study. Mice were maintained with 12 hr artificial light, 6–10 per cage and given Purina Chow and tap water ad lib. To eliminate the effect of diurnal cycles, if any, each day's studies routinely began 3 hr after the onset of light. Humane treatment of the animals was assured. Our colony is AALAC-approved and our experiments were designed to minimize discomfort.

Appearance/Toxicity/Seizures

The animals' appearance and gross behavior patterns were observed in their home cages prior to and after intraperitoneal (IP) injections of test compounds. Exploratory behavior and spontaneous motility were quantitated 1 hour after treatment by placing the test subject in a Motility Tester, Model 80, Bel Art Corp., Pequannock, NY. The tester consists of four runways equipped with metal floor plates. Each time the animal crosses from plate to plate a small current, undetectable to the animal, flows to a detector where it is amplified to register on a mechanical counter. The number of crossings during the first three minutes in the new surroundings serves as an indicator of exploratory behavior, the next ten minutes as an indicator of spontaneous motor activity (17). Mortality within 72 hr of treatment was used to estimate LD_{50}, the dose lethal in 50% of the subjects. A plot of dose vs. mortality was constructed and all points used in the calculation with the aid of commercial curve-matching computer software. Toxic side-effects (ataxia, motor impairment, neurological deficit) were determined 30 min after treatment using a rotorod treadmill (Ugo Basile, Comerio, Italy). Healthy animals had no difficulty remaining for 30 sec on the rotating rod. Inability to remain poised on the rotorod and/or time spent on it served as an indication of toxicity. Anticonvulsive effects were tested 90 min after treatment by subjecting the treated animals to electroshock applying alternating current for 0.3 sec with auricular electrodes in a Rahm Apparatus, Rahm Company, New York, NY, or by injecting them IP with 67 mg/kg of the chemoconvulsive agent pentamethylenetetrazol (Metrazol, Knoll). Seizure responses were rated on a scale of 0–5 points described earlier (1). All tests were performed double-blind.

Analgesia Tests

To minimize pain we routinely used a modified Randall-Selitto (RS) test in an Ugo Basile apparatus and used tail-flick and hotplate tests only to confirm the results obtained in the RS test. The Basile apparatus consists of a Teflon plinth and a pressure cone which tapers to a dull point that can be used to compress a person's finger (15), or an animal's paw or tail, with gradually increasing force (22). The end-point is recorded in units of weight applied. With a proper definition of the end-point, in our case, attempts to withdraw the tail, the subject experiences only mild discomfort. We placed the animal's tail rather than paw in the apparatus because we found that this decreased stress and provided us with more replicable indicia of discomfort. The test was carried out double-blind, in duplicate. The analgesia test was usually run 30 min after IP injection of 1 mg/kg or 5 mg/kg of the test substance or saline, but in a dose response study doses from 0.1 to 5 mg/kg were injected and in lethality studies doses up to 200 mg/kg were used. In time response and antagonism studies tests were run from 20 min to 1 week after treatment. In all cases, saline-treated controls were also run.

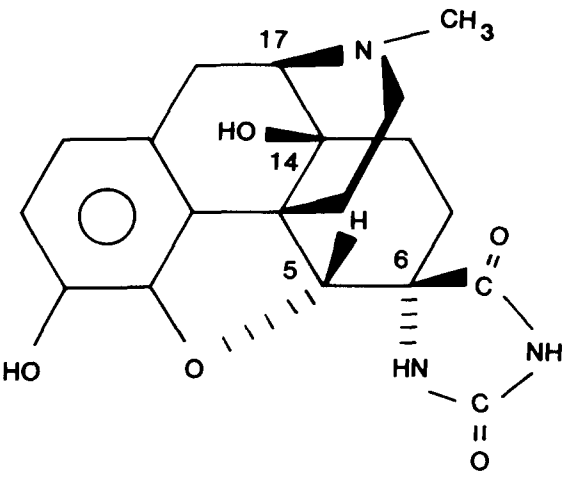

FIG. 1. Structure of oxymorphone-6-α-spirohydantoin.

Antagonist Effects

Baseline pain threshold in the RS test were determined prior to any treatment. Animals were then injected with the test compound or saline and retested 30 min later. To test for any residual agonist effects the animals' baseline pain threshold was measured again in 48 hr or at one week. Then, to test for antagonist activity, all animals were injected with morphine sulfate (5 mg/kg) or saline and retested 30 min after the injection. Each test for antagonist effects was carried in a fresh batch of animals.

Statistical Analysis

All values are means ± standard deviations. One-way analyses of variance were performed on all sets of data. Where the F-values indicated significant differences ($p<0.001$), all combinations of paired Student's *t*-values were calculated. Significant differences are shown in the tables. All statistical determinations were performed at the Psychiatric Institute Computer Center using commerical statistics software.

RESULTS

Synthesis

Oxymorphone-6α-spirohydantoin was synthesized and isolated as white crystals, m.p. 340°C in a yield of 50%. The purity of the compound was confirmed by elemental analysis and ^1H NMR spectra in D_2O which showed peaks at δ 6.66 (singlet, 2 H), 4.73 (singlet, 1 H) and 2.70 (singlet, 3 H). The structure assigned to the compound is shown in Fig. 1.

TABLE 1

TOXICITY AND ANTICONVULSIVE EFFECTS OF OXYMORPHONE AND ITS 6-SPIROHYDANTOIN DERIVATIVE

Treatment	Dose mg/kg	Rotorod sec	Exploratory Activity	Spont. Motility	Est. LD_{50}	Toxicity	Metrazol Seizures
Saline	—	30 ± 0	38.0 ± 5.5	31.7 ± 10.4	—	—	100%
Oxymorphone	1.0	30 ± 0	31.0 ± 8.0	3.0 ± 6.0		None	100%
	10	30 ± 0	114.7 ± 17.7*	322.0 ± 72.1*		None	100%
	100	0	8.0 ± 3.7	8.2 ± 11.3	x	Seizures	100%
Oxymorphone-6-spirohydantoin	1.0	30 ± 0	28.2 ± 8.7	33.5 ± 30.6		None	100%
	10	30 ± 0	25.0 ± 4.1	53.0 ± 14.9		None	50%
	100	12 ± 8	3.7 ± 4.8*	1.0 ± 2.0*		Lethargy	0%
	200	0	3.7 ± 5.7*	0*	x	Lethargy	0%

*$p<0.01$, Student's t-test, compared to saline controls.

Toxicity and Anticonvulsive Effects

Oxymorphone significantly altered the behavior of our animals. After injection of 10 mg/kg the animals became hyperactive, with the spontaneous activity rising dramatically (Table 1). Within 10 min of injection of 100 mg/kg, the animals became lethargic and some developed convulsions and succumbed in 3–5 hr. From a plot of dose vs. lethality we calculated the LD_{50} of oxymorphone in our mice at 100 mg/kg. The 6-spirohydantoin derivative of oxymorphone produced no observable behavior changes at 1.0 or 10 mg/kg. A dose of 100 mg/kg produced lethargy and decreased the animal's ability to stay on the rotorod, but produced no mortality. A dose of 200 mg/kg was 50% lethal.

The compounds did not protect the animals from electroshock seizures under our conditions, but the hydantoin derivative decreased the incidence of seizures induced by Metrazol (Table 1). The ED_{50} of oxymorphone, i.e., the dose which would have reduced seizures by 50%, was higher than 100 mg/kg, which was 50% lethal, but the ED_{50} of the oxymorphone-6-spirohydantoin was 10 mg/kg. Thus, introduction of the hydantoin moiety, which is conspicuously present in many anticonvulsive agents starting with phenytoin (diphenylhydantoin, Dilantin), enhanced the anticonvulsive properties of oxymorphone.

Agonist/Antagonist Activity

Morphine reduced pain sensitivity (raised pain thresholds) as measured in our modified Randall-Selitto test in a dose-related manner (Table 2). Both oxymorphone and its hydantoin derivative, at 5 mg/kg, produced an effect comparable to that of morphine. However, both compounds proved to be more effective than morphine at lower dose levels. At a dose of 0.1 mg/kg morphine had no observable effect, yet both oxymorphone and oxymorphone-6-spirohydantoin doubled the pain thresholds. At a dose of 1 mg/kg all three compounds had a similar effect in 30 min (Table 2), but the effect of the spirohydantoin derivative lasted for the full 3 hr of the experiment, while the effects of either morphine or oxymorphone waned after 30–60 min (Table 3).

Both oxymorphone and its 6-spirohydantoin derivative, which acted as analgesics 20–180 min after injection, were antagonistic to morphine 48 hr later. Pain thresholds reduced by morphine, oxymorphone or oxymorphone-6-spirohydantoin returned to pretreatment levels in 3–5 hr and were at baseline levels when tested in 48 hr. At that time some animals were injected with 5 mg/kg of morphine, others with saline and all were tested 30 min later. In subjects which had received placebo or morphine earlier, morphine now doubled the pain thresholds (Table 4). By contrast, in subjects which had received oxymorphone or oxymorphone-6-spirohydantoin, morphine had no analgesic effect. There was no increase in threshold; rather, the subjects appeared more alert to pain than at the start of the experiment. Thus, oxymorphone and its 6-spirohydantoin derivative, which had showed agonist activity at first, became antagonist with time. The antagonist effect of the 6-spirohydantoin derivative lasted longer than that of oxymorphone. At 48 hr both compounds displayed equal antagonist activity; at one week the effect of the parent compound disappeared, while the effect of the derivative remained significant ($p=0.0120$).

TABLE 2

COMPARISON OF AGONIST EFFECTS OF MORPHINE, OXYMORPHONE AND OXYMORPHONE-6-SPIROHYDANTOIN: DOSE RESPONSE

Drug	Pain Thresholds in g Pressure in the RS Test Dose (mg/kg) 0	0.1	1.0	5.0
Morphine	7.9 ± 1.4	8.2 ± 1.3	14.7 ± 3.2	25.0 ± 0
Oxymorphone	8.2 ± 2.0	16.2 ± 1.8*	16.3 ± 3.9	25.0 ± 0
Oxymorphone-6-spirohydantoin	8.4 ± 1.9	17.0 ± 5.8*	17.6 ± 3.2	22.2 ± 1.6

*$p<0.01$, Student's t-test, compared to morphine-treated animals.
0 dose: 10 ml/kg of physiologic saline.

TABLE 3

COMPARISON OF AGONIST EFFECTS OF MORPHINE, OXYMORPHONE AND OXYMORPHONE-6-SPIROHYDANTOIN: TIME EFFECT

Drug	Dose mg/kg	Pain Thresholds in g Pressure in the RS Test Time 20 min	60 min	180 min
Placebo	—	8.2 ± 3.5	8.5 ± 2.9	8.2 ± 2.3
Morphine	1.0	12.7 ± 6.3	10.7 ± 2.2	8.0 ± 1.5
Oxymorphone	1.0	16.4 ± 7.4	15.0 ± 3.5	9.1 ± 0.6
Oxymorphone-6-spirohydantoin	1.0	14.8 ± 4.8	16.2 ± 4.7	15.9 ± 4.1*

*$p<0.01$, Student's t-test, compared to morphine-treated animals.
Placebo: 10 ml/kg of physiologic saline.

TABLE 4

ANTAGONIST ACTIVITY OF OXYMORPHONE AND ITS 6-SPIROHYDANTOIN DERIVATIVE

Treatment No. 1 0 Time	Treatment No. 2 48 hr or 1 Week	Pain Thresholds (g pressure in the RS test) 48 hr Later Baseline	48 hr Later Posttreatment	One Week Later Baseline	One Week Later Posttreatment
Saline	Saline	7.8 ± 1.7	7.5 ± 1.7	7.3 ± 2.0	7.9 ± 3.0
Saline	Morphine	8.0 ± 2.8	16.3 ± 4.5	8.2 ± 1.7	16.1 ± 3.65
Morphine	Morphine	8.5 ± 1.9	14.1 ± 2.2	8.0 ± 1.9	16.1 ± 3.5
Oxymorphone	Morphine	6.1 ± 1.8	5.0 ± 1.7*	8.0 ± 2.9	15.3 ± 2.4
Oxymorphone-6-spirohydantoin	Morphine	5.3 ± 2.0	5.5 ± 3.0*	7.6 ± 1.2	10.4 ± 5.3*

*$p<0.015$, Student's t-test, compared to saline/morphine (line 2) animals. Each test (48 hr, 1 week) was carried out in a separate batch of test subjects. Drug dose in treatment No. 1 was 1 mg/kg, morphine dose in treatment No. 2, 5 mg/kg. Dose of saline, 10 ml/kg.

DISCUSSION

We have synthesized a 6-spirohydantoin derivative of the opioid analgesic oxymorphone and tested the new compound in vivo in mice to determine whether the introduction of the hydantoin moiety at the carbon-6 position of ring C altered the compound's toxicity, anticonvulsive effects and potency and/or duration of its agonist/antagonist activity. Our data indicate that the new compound is less toxic, much more anticonvulsive and significantly longer acting both as narcotic agonist and antagonist than oxymorphone.

In our mice, oxymorphone (1.0 mg/kg) led to a decrease in spontaneous activity; at the same dose the oxymorphone-6-spirohydantoin did not produce any changes in behavior. At 10 mg/kg, oxymorphone made the animals intensely hyperactive; the effect of the derivative, if any, was minor. A dose of 100 mg/kg of oxymorphone was 50% lethal. The derivative was 50% lethal at 200 mg/kg. Oxymorphone did not protect our mice from clonic-tonic seizures induced by the chemoconvulsive agent Metrazol, the derivative did. The dose effective in 50% of the subjects was 10 mg/kg in the case of the derivative; the dose for the parent compound could not be established because it was higher than the compound's 50% lethal dose, 100 mg/kg.

Both compounds exerted potent analgesic activity 20–60 min after an IP injection of doses ranging from 0.1 to 5.0 mg/kg. At a dose of 1.0 mg/kg the effect of the parent compound waned between 1–3 hr, the agonist effect of the derivative lasted longer than 3 hr. Our oxymorphone data confirm the findings of other investigators who found that its peak analgesic effect occurs at 30 min; our 6-spirohydantoin data parallels that for chloroxymorphamine or oxymorphazone which showed an analgesic effect 4 hr after injection and beyond (3, 10, 18). Whether the binding of the 6-spirohydantoin to the μ sites is irreversible as is that of oxymorphazone or chloroxymorphamine, but not that of oxymorphone itself (11), remains to be established. Binding μ sites by our 6-spirohydantoin in a nonequilibrium irreversible fashion would help explain our findings of a strong residual anticonvulsive effect 2 days after treatment.

After the initial agonist effects of both oxymorphone and its hydantoin derivative have fully worn off, i.e., at 48 hr after their injection, we found that both compounds antagonized morphine analgesia. Similar effects have been reported for oxymorphone and its chlorinated derivatives (3,19), although some of the temporal parameters in those studies differed significantly from ours. Caruso *et al.* (3) found that oxymorphone prevented morphine action when given 8 hr earlier but not when given 24 hr earlier. The antagonist effect of chloroxymorphamine lasted longer, decreasing gradually after 6 days. In our studies, oxymorphone prevented morphine action when given 48 hr prior, while the 6-spirohydantoin was antagonistic not only at 48 hr but also at 1 week. The different oxymorphone data can, of course, be due to the differences in experimental conditions, strain of animals, procedures of the analgesia assay, etc. The presence of the antagonistic effects, and their long duration after injection of various opioid derivatives, is more difficult to explain.

Substitutions at the C-6 position of the ring C of the opiate nucleus have a relatively modest effect on the agonist/antagonist properties of the compounds (5, 12–14, 16). Changes at this position usually "provide compounds retaining expected opioid activity" (13). We always felt, however, that addition of large polar moieties is likely to lead to slower penetrability and, therefore, to lower peak concentration in the brain and lower toxicity as well as to longer duration of action (8). Stronger affinity to a binding site or sites would also result in long-term blockage and longer period of action, as would induced modifications in the binding site. Induction of a time-specific cross-tolerance to morphine, suggested as one possible explanation of the latent antagonist effects of oxymorphone (3) may also have occurred. We find it difficult to accept another explanation for the mode of action of our spirohydantoin, namely the ability to bind multiple sites simultaneously as was suggested, for example, for β-funaltrexamine, with agonist activity at some sites (κ) and antagonist at others (μ) (3, 9, 19). It was claimed that in the case of the funaltrexamine the antagonist activity " . . . as a μ-receptor develops only after the weak κ-agonist effects . . . have worn off [(9), p. 231]. Our data do not indicate that the agonist activity of the oxymorphone-6-spirohydantoin is weak; in fact, it differs little from that of oxymorphone, although it is longer acting. Also, were both effects present at the same time, they would have counteracted each other to some extent—again we found no evidence that that is the case. We assume, therefore, as a working hypothesis, that the 6-spirohydantoin irreversibly binds morphine site(s), exerting agonist activity at first. The agonist activity wanes with time, but the sites continue to be blocked (or denatured) so that freshly injected morphine cannot exert its agonist effects. Whether the sites are actually bound or sterically modified and therefore unable to bind morphine remains to be determined. Also to be determined is the specific binding spectrum of our hydantoin or its in vivo metabolites. We assume that, like oxymorphone, the derivative binds μ sites. It is also likely that it binds κ sites, like β-funaltrexamine, binaltorphimine and norbinaltorphimine (21). The fact that the oxymorphone-6-spirohydantoin exerts a significant anticonvulsive effect might also be considered

as an indication that it is capable of binding κ sites (23), although the anticonvulsive activity reported for the κ receptors differed from that in the present study.

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