Pharmacology Biochemistry and Behavior, Vol. 63, No. 2, pp. 339–343, 1999
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0091-3057/99/$–see front matter

PII S0091-3057(99)00029-5

Evaluation of Intraarticular Opioid Analgesia for the Relief of Articular Pain in the Domestic Fowl

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Received 10 July 1998; Revised 27 January 1999; Accepted 27 January 1999

GENTLE, M. J., P. M. HOCKING, R. BERNARD AND L. N. DUNN. *Evaluation of intraarticular opioid analgesia for the relief of articular pain in the domestic fowl.* PHARMACOL BIOCHEM BEHAV **63**(2) 339–343, 1999.—An experimental paradigm, based on the microcrystalline sodium urate-induced arthritis pain model, was used to investigate the potential peripheral analgesic properties of a variety of opioid agonists. The response criteria were changes in behavioral profiles and pain-related behaviors over 60 min commencing 1 h after intraarticular injection. The testing system was used to determine the potential optimum dose of intraarticular application of morphine sulphate (1–3 mg), fentanyl citrate (0.5–3 mg), and buprenorphine hydrochloride (0.05–1 mg). None of the opioid analgesics used had any effect on pain behavior, and it was concluded that opioids with a high affinity for the mu receptor when injected intraarticularly were unlikely to be of use in the treatment or diagnosis of inflammatory arthritic pain in the strain of domestic fowl chosen. © 1999 Elsevier Science Inc.

Arthritis Sodium urate Domestic fowl Morphine sulphate Fentanyl citrate Buprenorphine hydrochloride

A high incidence of spontaneous arthropathies is common in heavy breeds of domestic poultry, leading to a loss of locomotor function (6–8,22). Preliminary studies have suggested that degenerative hip disorders in male breeding turkeys may be painful (9), but the painful consequences of other pathologies is unknown. In a model of acute gouty arthritis, both local anesthetic (15) and systemic steroid antiinflammatory drugs (unpublished observations) were effective in suppressing pain behavior, and are considered useful in the diagnosis of potentially painful joint disorders. Recent clinical studies in humans have shown that intraarticular injection of small systemically inactive doses of morphine provided effective long-lasting analgesia in patients undergoing orthopedic surgery (31,32). There are also a number of studies in animals demonstrating the peripheral effects of opioid activity (20,21,33), and opioid agonists are particularly effective in inflammatory pain. The potential benefits of the use of morphine, for example, as a peripheral analgesic is that the duration of analgesia is prolonged, and there are none of the side effects (e.g., drowsiness, mood change, respiratiory depression, nausia) seen with the higher doses usually given systemically. It has been shown in the rat that local administration of morphine or Met-enkephalin was 50–100 times more potent than the local anesthetic lidocaine (11), and there is the possibility of using intraarticular opioids for the diagnosis of joint pain.

A number of studies have used morphine for analgesia in the chicken, but the results have been contradictory. Schneider (28) tested the analgesic effect of morphine in chicks and found that the very high dose of 200 mg/kg had to be given intravenously to reduce the response to pinching the toe. More recently Fan et al. (10) demonstrated marked strain differences in response to morphine analgesia to a thermal stimulus applied to the skin on the top of the head. In one strain only 57% of the chicks showed analgesia with 100 mg/kg morphine, whereas another strain showed analgesia in all birds following 15 mg/kg of morphine injected intramuscularly. This sensitive strain was found to have had a sensitivity to morphine that approached that seen in mammals. Similar strain differences in analgesia to morphine were also observed by Hughes (16) using the latency to jump when birds were placed on a hot plate. Using the hot-plate test it was also found that doses of 5 and 10 mg/kg morphine did not produce analgesia but produced hyperalgesia, resulting in significant reductions in jump latencies (17,34). Most of the studies investigating morphine analgesia in birds have used acute nociceptive tests, but the one study in the pigeon using low doses of morphine

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(0.5–2.0 mg/kg) in a prolonged tonic pain test (intraarticular injection of talc in gum arabic) found that it was ineffective in the "one-footed position test" (2).

Experimentally induced acute gouty arthritis, produced by the intraarticular injection of sodium urate microcrystals, mimics naturally occurring gout, and has been demonstrated to be a reliable model for tonic inflammatory joint pain in the chicken (13–15). In a similar tonic pain model used in cats morphine reduced the pain-related behavior (23). The objective of the present study was to investigate the possible analgesic effects of intraarticular injection of opioids on pain-related behavior following sodium urate arthritis.

METHOD

Animals and Husbandry

Male chicks of a layer stock (ISA Brown) were obtained from a commercial hatchery at 1-day-old and reared in brooders for 3 weeks before being transferred to cages (500 mm wide × 400 mm deep) containing two to three birds. They were placed in individual cages (600 × 500 mm) at 10 weeks in the test situation and used for experiments at 12 weeks of age. The birds received a photoperiod of 14-h light and 10-h dark in every 24 h. Standard pelleted starter and grower diets, respectively, were fed ad lib from 0–6 weeks and 7 weeks to termination. Water was freely available from nipple drinkers at all times. A total of 216 birds were used and the average body weight of the birds at testing was 1.5 kg. All procedures were conducted under the UK Home Office project (60/1632) and personal (60/3500) licenses.

Experimental Treatments

Three of the commonly used opioid analgesics were selected for testing in Experiments 1 to 3. Two opioid agonists—morphine sulphate, fentanyl citrate—and one partial agonist—buprenorphine hydrochloride (Sigma, Poole, UK)—were used at a range of different doses in 1, 3, and 2 trials, respectively. Because these opioid analgesics have not been used previously for the treatment of arthritic pain in birds, the doses chosen for testing were based on previous work on other species and different routes of administration. Doses as low as 0.5–1 mg of morphine have been shown to produce effective analgesia for postoperative knee pain in man (31), and fentanyl given systemically has been reported to be 80 times more potent than morphine (24). Buprenorphine has been reported to be an effective analgesic in birds in doses of 0.01–0.05 mg injected intramuscularly (26). In the present experiment doses of opioids used were; morphine 1–3 mg, fentanyl 0.5–3 mg, buprenorphine 0.05–1.0 mg.

Experimental Methods

At 0915–0930 h the birds received an injection into the intraarticular space of the left hock joint from the plantar aspect using a 21-gauge needle. The urate-treated birds were injected with 0.2 ml of saline containing 6 mg sodium urate microcrystals prepared by the method of Seegmiller et al. (29), as described previously (15). At the same time, treated birds were injected with a specific quantity of the drug dissolved in 0.3 ml saline. Six birds were used on each treatment, and two control treatments of saline/saline and saline/highest dose of analgesic were performed in each experiment. The behavior of the birds was recorded for 1 h, commencing 1 h after injection.

Behavioral Observations

The birds were observed for 1 h behind a one-way screen by an observer who was not aware of the previous treatment of the bird. Bird activity was recorded every 5 min as standing, walking, feeding, drinking, grooming, resting awake, resting with eyes closed, dustbathing, and grooming while resting. Standing activities where the injected leg was raised were differentiated from two-legged activity or where the nontreated limb was raised.

Experimental Design and Statistical Analyses

Each experiment was a randomized block design with six blocks (three on each of 2 days) of six birds and different birds were used for all the treatments. The data were analyzed using a factorial model with treatment as the single factor. The dependent variables were analyzed as binomial variables (the total number of observations of an activity divided by 12) with extrabinomial variation modeled by the method of Williams (35). The combined data from different experiments with the same drug were analyzed using a polynomial response model after deleting the two control treatments. The means for these two groups were determined separately.

RESULTS

A number of behaviors were combined for analysis as described before (15): the proportions of time spent feeding, drinking, and pecking (oral activity); walking and standing (standing, sum of one- and two-legged behavior); and the proportion of time grooming while standing and resting (grooming). Dustbathing was rarely seen, and was grouped with grooming behavior. The proportion of time spent on one leg as a proportion of time on all standing activities was also analyzed. The overall proportion of time spent on oral, grooming, resting, and standing behaviors for birds on different treatments are reported in the tables.

Morphine

The results for birds given urate were similar regardless of the administration of morphine (Table 1). The birds given 3 mg morphine without urate spent less time standing than the control group ($p < 0.05$). The administration of urate with or without morphine greatly decreased oral and grooming behavior, and the major activities of these birds was passive, sitting or standing on one leg. There was no statistically significant relationship between the dose of morphine and behavior.

Fentanyl

An apparent response to fentanyl in trial 1 was not confirmed in trials 2 and 3. The mean proportions of observations on different activities are shown in Table 2. The behaviors of birds on the three control (highest) drug doses evaluated without urate were similar, and are presented as a single mean. Fentanyl per se had no detectable effect on any behavior, and did not restore the behavioral profile of birds given urate injection over the range of doses studied.

Buprenorphine

The injection doses of buprenorphine were 0.00, 0.010, 0.025, and 0.050 mg in trial 1a and 0.1, 0.25, and 0.5 mg in trial 1b (three birds per treatment). In trial 2 the doses were 0.00, 0.50, 0.75, and 1.00 mg. The predicted means at several injection doses from regression analysis of the combined data are

TABLE 1

MEAN PROPORTIONS OF TIME (%) FOR DIFFERENT BEHAVIORAL ACTIVITIES OF BIRDS GIVEN DIFFERENT DOSES OF INTRAATRICULAR INJECTIONS OF MORPHINE SULPHATE WITH AND WITHOUT URATE MICROCRYSTALS

Treatment		Behavior (Proportion of Observations)									
		Oral‡		Grooming¶		Standing		Resting		One-Legged Standing#	
Morphine* (mg)	Uric Acid†	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
(a) Effect of morphine per se											
0	−	16.7	4.5	18.1	5.1	18.1	4.6	47.2	7.5	54.0	8.4
3	−	11.1	3.8	19.4	5.2	6.9	3.1	62.5	7.3	36.9	12.3
χ^2, 1 *df*		0.7		0.0		11.7**		2.1		1.1	
(b) Evaluation of morphine analgesia											
0	+	1.4	1.4	4.2	2.7	18.1	4.6	76.4	6.3	91.4	9.4
1	+	2.8	2.0	6.9	3.4	6.9	3.1	83.3	5.6	98.6	6.7
2	+	0.0	0.0	1.4	1.6	11.1	3.8	87.5	5.0	87.8	6.1
3	+	2.8	2.0	5.6	3.1	9.7	3.6	81.9	5.8	86.0	8.1
Regression ± SE (%/mg)		0.083 ± 0.375		−0.033 ± 0.290		−0.213 ± 0.207		0.146 ± 0.175		−0.155 ± 0.155	

*Morphine sulphate in 0.3 ml saline.
†− = 0.2 ml saline; + = 6 mg urate microcrystals in 0.2 ml saline.
‡Feeding, drinking, and pecking (standing).
¶Grooming while standing and resting.
#As a percentage of time spent standing.
**$p < 0.001$.

presented in Table 3. There was a significant response in oral behavior in the combined data that was largely the result of one animal given 1 mg dose (feeding in 5 of 12 observations). The predicted means for the other behaviors reflect this, and although numerically interesting, the regression coefficients were not significantly different from zero. The behaviors of birds on the three control (highest) drug doses evaluated without urate are presented as single means (Table 3). Birds given buprenorphine without urate spent more time sitting and less time standing compared with the controls ($p <$ 0.001). The proportion of the time spent sitting in urate- and buprenorphine-treated birds were similar (Table 3).

TABLE 2

MEAN PROPORTIONS OF OBSERVATIONS (%) FOR BEHAVIORAL ACTIVITIES OF BIRDS GIVEN DIFFERENT DOSES OF INTRAARTICULAR INJECTIONS OF FENTANYL CITRATE WITH OR WITHOUT SODIUM URATE MICROCRYSTALS (COMBINED DATA FROM THREE TRIALS).

Treatment		Behavior									
		Oral‡		Grooming¶		Standing		Resting		One-Legged Standng#	
Fentanyl*	Uric acid†	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
(a) Effect of fentanyl per se											
0	−	15.7	2.2	13.4	2.6	30.6	3.5	40.3	4.5	42.0	5.0
0.8/1.0/3.0	−	11.1	1.9	15.3	2.7	36.6	3.7	37.0	4.5	44.4	5.4
χ^2, 1 *df*		2.5		0.3		1.4		0.3		0.1	
(b) Effect of fentanyl analgesia											
0.0	+	3.4	1.0	7.4	1.4	21.6	2.6	67.6	2.9	64.7	5.2
0.5	+	3.2	0.6	7.9	1.0	21.9	1.8	67.1	2.1	64.4	3.6
1.0	+	2.9	0.6	8.5	1.1	22.1	1.8	66.6	2.0	64.2	3.3
1.5	+	2.7	0.7	9.1	1.6	22.4	2.6	66.0	2.8	64.0	4.7
2.0	+	2.5	0.9	9.7	2.3	22.6	3.7	65.5	4.0	63.8	6.7
2.5	+	2.3	1.1	10.4	3.3	22.9	4.9	65.0	5.3	63.6	9.0
3.0	+	2.2	1.3	11.1	4.3	23.2	6.2	64.4	6.7	63.4	11.4
Regression (χ^2, 1 *df*)		−0.162 ± 0.276		0.160 ± 0.204		0.033 ± 0.169		0.053 ± 0.142		−0.031 ± 0.362	

*Fenanyl citrate treatment.
†C = control (0.2 ml saline); UA = 6 mg uric acid in 0.2 ml saline.
‡Feeding, drinking, and pecking (standing).
¶Grooming while standing and resting.
#As a percentage of time spent standing.

TABLE 3

MEAN PROPORTIONS OF OBSERVATIONS (%) FOR DIFFERENT BEHAVIORAL ACTIVITIES OF BIRDS GIVEN DIFFERENT DOSES OF INTRAATRICULAR INJECTIONS OF BUPRENORPHINE HYDROCHLORIDE WITH AND WITHOUT URATE MICROCRYSTALS (COMBINED DATA FROM THREE TRIALS)

Treatment		Behavior (Proportion of Observations)									
		Oral ‡		Grooming¶		Standing		Resting		One-Legged Standing #	
Buprenorphine mg*	Uric acid†	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
(a) Effect of buprenorphine per se											
0	−	13.5	3.0	16.0	2.5	30.2	4.2	40.3	4.6	8.2	2.0
(0.05,0.50,1.0)	−	5.1	2.7	21.0	6.5	5.0	2.6	79.5	5.7	83.0	3.9
χ^2, 1 *df*		3.2		0.5		16.3‡‡		14.8‡‡		7.5††	
(b) Effect of buprenorphine analgesia											
0	+	0.0	0.0	2.8	1.7	13.9	5.2	83.3	5.3	81.6	15.0
0.03a	+	0.0	0.0	2.0	1.4	5.3	4.4	93.0	5.0	0.0	1.0
0.30b	+	0.0	0.0	9.3	4.6	9.4	6.9	79.5	9.4	13.9	13.3
0.50	+	1.4	1.6	6.9	3.3	11.1	4.4	80.6	5.5	69.7	2.1
0.75	+	0.0	0.0	26.4	5.7	11.1	4.4	62.5	6.8	47.7	25.6
1.00	+	6.9	3.3	13.9	4.5	11.1	4.4	68.1	6.5	79.1	18.6
Regression ± SE (%/mg)		5.81 ± 2.16**		0.91 ± 0.54		−0.31 ± 0.50		−0.60 ± 0.42		2.91 ± 1.78	

*Buprenorphine hydrochloride in 0.3 ml saline.
†− = control (0.2 ml saline); + 6 mg uric acid in 0.2 ml Haemaccil.
‡Feeding, drinking, and pecking (standing).
¶Grooming while standing and resting.
#As a percentage of time spent standing.
(a) Mean for trial 1A (doses 0.010, 0.022, and 0.050 mg in 0.3 ml saline).
(b) Mean for trial 1B (doses 0.10, 0.25 and 0.50 mg in 0.3 ml saline).
**$p < 0.05$; ††$p < 0.01$; ‡‡$p < 0.001$.

DISCUSSION

Although both local anesthetic (15) and systemic steroid antiinflammatory drugs (unpublished observations) produced supression of pain behavior in sodium urate arthritis, none of the three opioid analgesics injected intraarticularly had any analgesic effects on tonic pain in the present experiment. One possible reason for the lack of effect was that the dose chosen was too small. This seems unlikely, because 1 mg of morphine was sufficient to produce effective relief of postoperative knee pain for up to 48 h in human patients (31), and both fentanyl and buprenorphine are significantly more effective opioid agonists than morphine. There were also problems in administering higher doses of the drugs because of their solubility in relation to both the relatively small size of the avian ankle joint and the small volume of fluid that could be injected. This was more of a problem with buprenorphine than with morphine and fentanyl, but solubility nevertheless limited the highest concentration that could be injected.

Animal models of inflammation have shown that local injections of small doses of opioids into inflammed sites produces potent analgesia, yet the same doses given systematically or into uninflammed sites are without effect (30). Peripheral opioid effects are, therefore, not obvious in normal tissue, but become so within minutes to hours after the start of inflammation (1,27,30): the mechanisms for these effects are not understood. The sodium urate arthritis used in the present experiment produced a marked inflammatory response, together with sensitization of joint capsule C-fiber nociceptors (13). The pharmacology of sodium urate arthritis is similar in birds and mammals (3–5,12,23) and sodium salicylate, acetaminophen, colchicine, and steroidal antiinflammatory drugs are effective analgesics in both groups of animals. Opioids are effective analgesics in the rat (5), cat (23), and humans (29), but they were not effective in the present experiment on the chicken, suggesting a clear difference between birds and mammals. The use of alternative inflammatory models such as turpentine (18) or carrageenan (19) demonstrated that in these models the acute inflammatory response of the chicken differed from that in the mammal. Ito et al. (19) has suggested that in carrageenan-induced inflammation histamine and serotonin play a major role rather than the kinin system, which is the main inflammatory mediator in the rat. If sodium urate arthritis produced a similar pattern of inflammation as terpentine and carrageenan, then the failure of opioids to affect inflammatory pain in birds may be related to the absence of bradykinin and prostaglandin activation.

Systemic morphine affects the behavior of the chicken even at doses as low as 2.5 mg/kg bodyweight. The behavioral changes are usually a sleep-like posture with eyes closed and the head held down (16), and at higher doses of 15 mg/kg there is ataxia and sedation (10). In the present experiment, fentanyl did not produce any behavioral evidence of systemic effects, whereas morphine at the highest dose of 3 mg (equivalent to 2 mg/kg) produced a reduction in standing, although the increase in resting behavior was not significant. Buprenorphine, on the other hand, at doses from 0.05 to 1.0 mg produced significant behavioral changes in the birds, with a reduction in standing and an increase in resting. These behavioral changes, resulting from buprenorphine injection alone, confounded the interpretation of the effects of buprenorphine on sodium urate arthritis. Of the behaviors used to measure pain following urate arthritis, one-leg standing has been used as a reliable indicator (2–4,12,14). Of the opioids tested in the absence of arthritis, only buprenorphine produced a significant increase in

one-legged standing. An alternative explanation for the behavioral changes produced by buprenorphine alone may be that it induced a hyperalgesia. Hyperalgesia has been reported following low doses of morphine (16,17,33) injected intramuscularly in chicks, but there have been no reports on the effects of buprenorphine.

In conclusion, it would appear that the three opioids used in this experiment did not produce any significant analgesia following intraarticular injection in the strain of birds used in this study. Considering the large strain differences in response to morphine reported in other studies (10,16) it is too early to speculate on the use of opioids as part of any experimental design for investigating the pain of inflammatory arthritis in the domestic fowl. All three opioids have a high affinity for the mu receptor, and the results do not exclude the possibility of other drugs such as kappa-opioid agonists from being effective (25).

ACKNOWLEDGEMENTS

This research was conducted as part of a commission form the UK Ministry of Agriculture Fisheries and Food.

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