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The pharmacology of azidomorphine and azidocodeine

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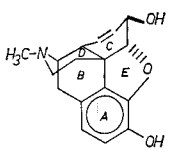
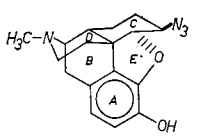
From a series of newly synthesized morphine derivatives 6-deoxy-6-azidodihydroisomorphine (azidomorphine) and 6-deoxy-6-azido-dihydroisocodeine (azidocodeine) were selected for detailed pharmacological study. In the hot plate test in rats, azidomorphine proved to be about 300 times and azidocodeine about 13 times more potent than morphine. Azidomorphine given over ten weeks was significantly less toxic in the rat than morphine or fentanyl. A total dose 40 times that of the analgesic ED50 dose of morphine (200 mg kg^{-1}) produced the highest grade physical dependence in mice as measured by naloxone-precipitated jumping. However, even a total dose of 2800 times the analgesic ED50 dose of azidomorphine (70 mg kg^{-1}) was less effective in producing physical dependence. Treatment on every second day with increasing doses of morphine led to the development of high grade tolerance and chronic physical dependence in rats and monkeys (*Rhesus macacus*). Severe abstinence syndrome was precipitated after the administration of nalorphine in rats pretreated for 24 days with rapidly increasing doses of morphine and grave symptoms of abstinence were elicited in pretreated monkeys on withdrawal of morphine on the 55th, 175th and 300th days of treatment. In parallel experiments neither the development of tolerance nor that of physical dependence was demonstrable in rats and monkeys pretreated with increasing equi-analgesic doses of azidomorphine.

In the search for morphine derivatives of high potency and having a more advantageous spectrum of activity than the parent molecule (I), 6-deoxy-6-azido-dihydroisomorphine (azidomorphine; II) and 6-deoxy-6-azido-dihydroisocodeine (azidocodeine), synthesized by Bognár & Makleit (1968), were selected from a series of new morphine derivatives. A comparison of their actions with those of morphine is now reported.



I Morphine



II Azidomorphine

METHODS AND MATERIALS

Toxicity

The test compound as base, was dissolved in 5% phosphoric acid and the pH of the solutions was adjusted to 6 with N NaOH. This solution was administered (5 ml kg^{-1} i.v. or s.c. or 10 ml kg^{-1} orally) to Wistar rats, 120–150 g, of either sex. The LD50 was calculated according to Litchfield & Wilcoxon (1949).

Analgesic effects

Hot plate test. The method of Woolfe & McDonald (1944) modified by Pórszász & Herr (1950) was used. The animals were placed on a hot plate (56°) before and 20, 30 and 60 min after intravenous, subcutaneous, or oral administration of the compounds. A reaction time 2·5 times that of the control value was considered as 100% effect. Each dose was tested on at least 10 animals and the ED50 was calculated on the basis of the dose-response curve.

Tail flick method of D'Amour & Smith (1941). Before administration of the test compound the tail flick response of the untreated animal (which we found to be usually 3–5 s) was determined with 0·1 s accuracy and the dose of the drug given was considered to exert an analgesic action if 30 min after subcutaneous administration the animal failed to respond by withdrawing its tail over a period twice as long as its own control response time. Each dose was tested on at least 10 rats and the ED50 was calculated on the basis of the dose-response curve.

Writhing test. The method of van der Wende (1956) modified by Witkin, Heuber & others (1961) and Koster & Anderson (1963) for mice was used. Each dose of test compound was administered to a group of 10 mice, and, after 15 min, a 0·6% acetic acid solution (60 mg kg^{-1}, i.p.) was injected. The characteristic response was observed in 90% of the control animals. The animals treated with the analgesic were kept under observation for 20 min after injection of the irritant and it was taken as an analgesic effect if during this interval no writhing occurred.

The analgesic effect of the individual doses was expressed as a percentage:

$$\% \text{ analgesic effect} = 100 - \frac{\text{writhing treated } \%}{90\%^*} \times 100$$

Each dose was tested in groups of 15 mice and the ED50 was calculated on the basis of the dose-response curve.

Potentiation of anaesthesia

Wistar rats of either sex, 120–150 g, were randomly assigned to groups of ten. The duration of anaesthesia produced by Venobarbital (Inactin, 5-ethyl-5-(1-methyl-propyl)2-thiobarbituric acid, sodium salt), 35 mg kg^{-1}, was considered as the control sleeping period. Venobarbital in physiological saline was injected into the tail vein at a volume of 5 ml kg^{-1}. The duration of anaesthesia was expressed as the time elapsed between the loss and reappearance of the "righting" reflex. ED500% and ED1000% represent doses causing five- or tenfold prolongation of anaesthesia as compared to control values determined on the same day. The range of control sleeping time was 520 to 960 s.

Respiratory effects

Frequency and amplitude of respiration in rabbits, 3·5–5 kg, were registered by means of a Marey tambour on a smoked drum. The test compounds dissolved in physiological saline were injected (0·5 ml kg^{-1}). Control measurements were made for at least 1 h preceding the administration of the test compound and the changes of respiration were registered over 3 h. The effect of each dose was tested on at least

* On the basis of preliminary examinations and the relevant literature (Hendershot & Forsaith, 1959).

3 rabbits and the doses causing 50% reduction in the frequency of respiration were calculated.

Circulatory effects

Cats of either sex, 2–3 kg, were anaesthetized with chloralose (30 mg kg^{-1}) and urethane (200 mg kg^{-1}). Blood pressure was registered by means of a mercury manometer, respiration by a Marey tambour, and contractions of the nictitating membrane were recorded by an auxotonic writing lever on a kymograph. Blood pressure in the right common carotid was measured; the test substance in 1·0 ml physiological saline was injected into the left femoral vein. Most experiments were made with artificially respired animals. Blood clotting was inhibited by injection of heparin (5 mg kg^{-1}) into the femoral vein at the beginning of the experiment. To test the effect of carotid occlusion both common carotids were exposed, vagotomy was performed and blood pressure was measured in the right femoral artery while the test substance was injected into the left femoral vein. The simultaneous occlusion of both common carotids lasted for 45 s. Circulatory effects were studied in the following steps: (i) stimulation of the central stump of the vagus; (ii) intravenous injection of 5 μg kg^{-1} acetylcholine; (iii) intravenous injection of 5 μg kg^{-1} adrenaline; (iv) carotid occlusion.

Effects on impulse transmission

Cervical ganglion of the cat. The cat superior ganglion was isolated and electrodes placed on the pre- and postganglionic section of the sympathetic nerve. The lingual artery was exposed for injection according to Trendelenburg (1957).

During the intra-arterial injections, the ipsilateral external carotid artery was occluded. The effect of the drug on sympathetic transmission was assessed by measuring the auxotonic contractions of the nictitating membrane elicited by pre- and postganglionic stimulation.

Longitudinal muscle strips of the guinea-pig ileum, isolated according to Paton & Vizi (1969), were suspended in 3·5 ml Krebs solution of 37° gassed with 5% carbon dioxide in oxygen. Stimulation was at 0·1 Hz. Supramaximal stimuli (potential drop: 8 V cm^{-1}) of 1 ms duration were applied. Contractions caused by acetylcholine released by "field" stimulation were registered isometrically by means of a penwriter (Servogor).

Physical dependence

Mouse. The development of acute physical dependence in the mouse was measured by the method of Saelens, Granat & Sawyer (1972). The test is based on the original observations of Huidobro & Maggiolo (1965) that mice dependent upon morphine show an uncontrollable urge to jump when treated with a morphine-antagonist.

The effects of different dose schedules of morphine and azidomorphine (10 ml kg^{-1}; i.p.) were studied in a 2 day test. In the mice pretreated with 7 doses of morphine or azidomorphine during 26 h, the number of jumps (all 4 paws off the bottom surface) precipitated by 100 mg kg^{-1} of nalorphine hydrochloride or 100 mg kg^{-1} of naloxone hydrochloride was counted.

Rat. The development of chronic physical dependence was measured by Buckett's method (1964) in rats, 60–70 g. Groups of 30 to 50 animals were treated with intra-

peritoneal doses of the test substance at 9 a.m. and again at 3.30 p.m. The doses were increased over 11 days and this was followed by maintenance treatment. Physiological saline was similarly injected into ten control animals. The development of physical dependence was assessed on the 12th, 18th and 24th day of the treatment. Abstinence syndrome was precipitated by the intraperitoneal administration of 10 mg kg^{-1} nalorphine hydrochloride instead of the morning dose of the analgesic. The abstinence symptoms were scored in the following way: writhing 3, squealing 2, diarrhoea 2, teeth chatter 1, ptosis 1, "Wet dog" 1. This indicates that maximum 10 points could be scored.

Monkey. Groups of six monkeys (*Rhesus macacus*), 7–8 kg, were injected the compounds subcutaneously at 9.30 a.m. and again at 4 p.m. Abstinence syndrome was elicited by the withdrawal of the analgesic. Physical dependence was tested 48 h after the last injection. The strength of the abstinence syndrome was determined according to Seevers & Deneau (1963).

Drugs used. Morphine hydrochloride and nalorphine hydrochloride (Alkaloida), naloxone hydrochloride (Endo Lab.), fentanyl (Janssen Pharmaceutica), pethidine hydrochloride (Chinoin), ethylmorphine hydrochloride, codeine hydrochloride (Alkaloida), ethylmethylpropylthiobarbituric acid (Venobarbital, Chinoin), acethylcholine iodide (BDH), adrenaline hydrochloride (Tonogen, Gedeon Richter), 6-deoxy-6-azidodihydroisomorphine base (azidomorphine), and 6-deoxy-6-azidodihydroisocodeine base (azidocodeine, Alkaloida), mepyramine maleate (May & Baker).

RESULTS

Toxicity

The acute toxicity of azidomorphine and azidocodeine compared to morphine and other analgesics in rats is shown in Table 1. Morphine proved to be about 40 times less toxic than azidomorphine, however, in analgesic activity azidomorphine is about 300 times more potent (see data in Tables 1 and 2). The toxicological data are in good agreement with those of Finnegan, Haag & others (1948), Kiessel, Albert & Boxill (1961) and Harris & Pierson (1964). Fig. 1 demonstrates that chronic treatment with azidomorphine is safer than with morphine or fentanyl at doses having equipotent analgesic activity.

Table 1. *The acute toxicity (in the rat) of azidomorphine and azidocodeine compared to known analgesics.*

Compound	Toxicity LD50 (mg kg^{-1})		
	i.v.	s.c.	oral
Morphine	320 (271·1–377·6)	310 (267·2–349·6)	1200 (937·5–1536·0)
Ethylmorphine	62 (52·9– 72·5)	200 (172·4–232·0)	810 (729·7– 899·1)
Codeine	75 (70·7– 79·5)	190 (143·9–250·8)	650 (560·0– 754·0)
Pethidine	62 (58·9– 65·2)	280 (194·4–403·2)	290 (245·7– 342·2)
Methadone	11 (9·3– 12·98)	28 (24·5– 31·9)	—
Pentazocine	21 (14·2– 30·9)	280 (241·3–328·8)	340 (288·1– 401·2)
Fentanyl	6 (4·6– 7·7)	12 (7·9– 19·6)	18 (9·4– 34·2)
Azidomorphine	8·1 (7·7– 10·4)	13 (11·7– 19·0)	62 (49·2– 73·2)
Azidocodeine	52 (49·2– 54·9)	125 (100·0–156·2)	120 (93·3– 154·2)

Values in brackets indicate 95% confidence limits.

Table 2. *The analgesic activity of azidomorphine and azidocodeine compared to some known analgesics.*

Compound	Hot plate test (rat) ED50 mg kg^{-1} i.v.	s.c.	oral	Therapeutic index LD50 s.c. / ED50 s.c.	Tail flick test (rat) ED50 mg kg^{-1} s.c.	Therapeutic index LD50 s.c. / ED50 s.c.	Writhing test (mouse) ED50 mg kg^{-1} s.c.	Therapeutic index LD50 s.c. / ED50 s.c.
Morphine	4·3 (2·6–7·9)	4·7 (2·9–7·8)	84·0 (56·3–125·7)	66	1·8 (1·08–3·15)	172·2	0·69 (0·65–0·76)	449
Fentanyl	0·028 (0·025–0·031)	0·032 (0·02–0·051)	1·8 (1·17–276)	375	0·024 (0·021–0·028)	500	0·032 (0·022–0·045)	375
Codeine	6·9 (5·1–9·2)	14·00 (6·7–29·4)	112·5 (53·5–236·3)	13·6	22·0 (15·3–28·8)	8·6	9·8 (7·59–12·64)	19·4
Pethidine	2·2 (1·4–3·3)	4·9 (4·1–5·5)	32·0 (19·6–48·9)	57·1	4·3 (2·7–6·6)	65·1	3·3 (1·59–6·93)	85
Methadone	0·59 (0·4–0·7)	1·9 (1·4–2·5)	8·1 (6·0–10·9)	14·7	1·6 (1·1–2·3)	17·5	0·71 (0·48–1·05)	39·4
Azido-morphine	0·015 (0·011–0·020)	0·016 (0·0067–0·038)	9·2 (6·0–12·9)	812·5	0·012 (0·0089–0·016)	1083	0·013 (0·009–0·018)	1000
Azido-codeine	0·32 (0·19–0·52)	0·36 (0·16–0·79)	13·5 (10·5–16·3)	347·2	0·61 (0·41–0·79)	205	0·41 (0·256–0·656)	305
Pentazocine	4·6 (3·86–5·47)	9·1 (4·78–17·29)	48·0 (22·8–60·8)	30·8	12·2 (8·1–18·3)	23·0	8·1 (5·46–12·3)	34·6

In parentheses: 95% confidence limits.

Analgesic effects

The data in Table 2 indicate that both azidomorphine and azidocodeine are more potent analgesics than morphine.

In rats on subcutaneous administration the azidomorphine: morphine analgesic ratio was 150 in the tail flick and 293 in the hot plate test. The corresponding values with azidocodeine were 13 for the hot plate, and about 3 for the tail flick test.

Comparison of the median therapeutic indices (LD50: ED50) shows that azidomorphine possesses a very favourable safety margin when given either intravenously (LD50: ED50–540) or subcutaneously (812) and is significantly superior to morphine (see Tables 1 and 2).

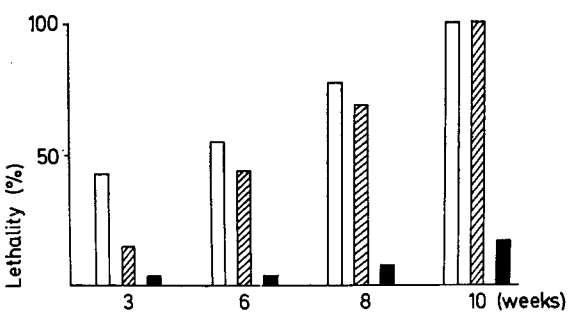


FIG. 1. Comparison of the toxicity of daily increasing doses of azidomorphine (solid columns), morphine (hatched columns) and fentanyl (open columns) in groups of 30 rats. Treatment started with two daily s.c. doses of 20 mg kg^{-1} morphine, and 50 μg kg^{-1} azidomorphine or fentanyl. The daily dose of morphine was increased by increments of 2 × 10 mg kg^{-1} and that of azidomorphine and fentanyl by 2 × 25 μg kg^{-1}.

Table 3. *The potentiating effect of azidomorphine, azidocodeine, morphine and fentanyl on Venobarbital* anaesthesia.*

Compound	Route of administration	Dose (μg kg^{-1})	Time**	Prolongation of sleeping time (%)***	ED500%**** (μg kg^{-1})	LD50 / ED500%	ED1000**** (μg kg^{-1})	LD50 / ED1000%
Azidomorphine	i.v.	10	5	714				
		25	5	620				
		25	30	278	10	810	60	135
		25	60	159				
		50	5	900				
		75	5	1166				
		100	5	1619				
Azidocodeine	i.v.	50	5	591				
		100	5	934	50	1040	150	350
		200	5	1135				
	s.c.	200	30	250				
		400	30	418	500	250	900	140
		600	30	763				
		1000	30	1266				
Morphine	i.v.				2500	144	10000	36
Fentanyl	i.v.	10	5	324				
		20	5	612	15	500		
		30	5	547				

* The dose of Venobarbital was 35 mg kg^{-1} i.v.
** Time (min) between the administration of the narcotics and that of Venobarbital.
*** The average sleeping time produced by Venobarbital (35 mg kg^{-1}, i.v.) was determined on the same day taken as 100%.
**** Indicates the dose of narcotic that will increase sleeping time by 500 and 1000% respectively.

Potentiation of anaesthesia

The anaesthesia-potentiating effect in rats of azidomorphine and azidocodeine compared to that of morphine and fentanyl is seen in Table 3. The order of potency of the compounds in this test was similar to that found in the analgesic tests.

Respiratory effect

Like morphine, azidomorphine and azidocodeine depressed the frequency and amplitude of respiration in rabbits. At intravenous administration the doses required to produce 50% depression were (mg kg^{-1}) 5·1 for morphine, 0·018 for azidomorphine and 0·190 for azidocodeine.

Circulatory effects

When administered at doses of 20–40 μg kg^{-1} to cats azidomorphine caused a fall in blood pressure of 20–40 mm Hg. It failed to antagonize the effects of vagal stimulation, acetylcholine, adrenaline infusion or carotid occlusion. As with morphine (Feldberg & Paton, 1951) the hypotensive effect appeared to be partly the result of histamine release. This is evidenced by the fact that the intravenous administration of 1 mg kg^{-1} of mepyramine partly prevented the hypotensive action of the azido derivatives. However, the hypotensive effect of azidocodeine was 10 times weaker than that of azidomorphine.

Effects on the transmitter systems

Azidomorphine injected into the lingual artery in a dose of 0·5–3 μg per cat inhibited the contractions of the nictitating membrane produced by preganglionic sympathetic stimulation (Fig. 2). However, the responses to postganglionic stimulation and adrenaline injected into the femoral vein (10 μg kg^{-1}) were not influenced. This

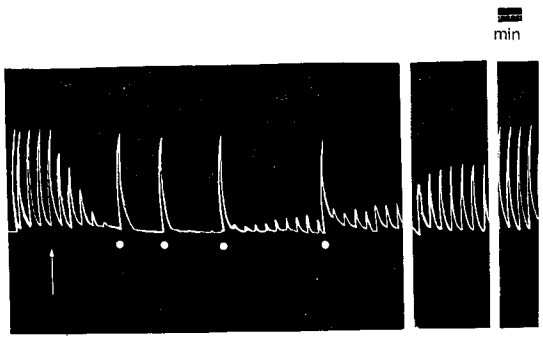


FIG. 2. Effect of azidomorphine (2×10^{-6} g) injected at ↑ into the lingual artery on the contractions of the nictitating membrane in the cat. Auxotonic recording. Preganglionic stimulation (5 V, 0·2 m s, 10 Hz for 5 s). Dots indicate postganglionic stimulation. Note the inhibition by azidomorphine of responses of nictitating membrane to preganglionic stimulation.

observation is consistent with that of Trendelenburg (1957) who showed this for morphine. However, Kosterlitz & Wallis (1966) observed that morphine inhibited the transmission in the superior cervical ganglion only at high concentration. This effect is probably due to the inhibition of acetylcholine release.

Small doses of morphine that are known to reduce significantly the output of acetylcholine in the longitudinal muscle (Paton, 1957) inhibit, while larger doses increase, contractions of the longitudinal muscle strip of the guinea-pig ileum elicited by 0·1 Hz stimulation. A similar pattern was seen with azidomorphine. This observation is in agreement with those of Paton (1957) and Gyang & Kosterlitz (1966) and Fennessy, Heimans & Rand (1969) who showed that in guinea-pig isolated ileum tachyphylaxis developed to morphine-like analgesics. It has been reported by Paton (1957) that, although morphine depresses twitches of the guinea-pig ileum, if concentrations are increased, the depressant action diminishes. Azidomorphine was about a hundred times more effective than morphine in its ability to decrease the contraction (Fig. 3). This effect of azidomorphine, like that of morphine, is due to its presynaptic inhibitory action on acetylcholine release, as evidenced by Knoll, Fürst & Vizi (1973).

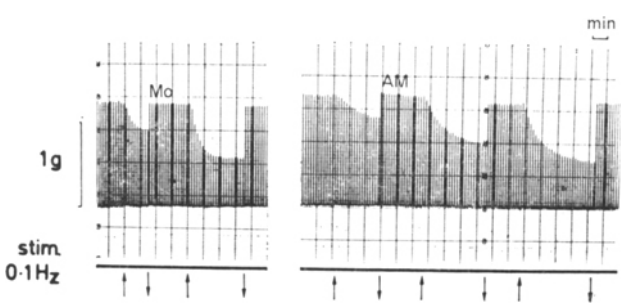


FIG. 3. Effect of morphine Mo ($1{\cdot}3 \times 10^{-8}$ and $1{\cdot}3 \times 10^{-7}$ M) and azidomorphine AM ($3{\cdot}2$, $6{\cdot}4 \times 10^{-10}$, $11{\cdot}3 \times 10^{-9}$ M) on the at ↑ contractions of the longitudinal muscle strip of guinea-pig ileum in response to field stimulation. Supramaximal field stimulation (10 V cm^{-1}, 1 ms) was applied as indicated. Note the inhibitory action of morphine and azidomorphine on contractions. Drugs were administered every 30 min in Krebs solution, 95% O_2 + 5% CO_2. Isometric recording system. (↓ Wash out).

Table 4. *Physical dependence liability of morphine and azidomorphine in mice (2 day test results in the mouse jumping test).*

Compound	Total dose (mg kg^{-1})	Total** dose: Analgesic ED50*	Naloxone challenge (100 mg kg^{-1} on day 2 at 1 p.m.): Average jumps per mouse	Naloxone challenge (100 mg kg^{-1} on day 2 at 1 p.m.): No. of mice jumped/ No. of mice tested	Nalorphine challenge (100 mg kg^{-1} at 1 p.m.): Average jumps per mouse	Nalorphine challenge on day 2: No. of mice jumped/ No. of mice tested
Morphine	100	20	9·7	20/25	—	—
	200	40	46·4	25/25	—	—
	400	80	42·7	25/25	—	—
	1000	200	48·7	25/25	13·9	38/50
Azidomorphine	1	40	0·0	0/25	—	—
	10	400	1·4	10/25	—	—
	40	1600	10·1	19/25	—	—
	70	2800	7·4	12/25	5·2	25/50

* Hot plate test. ED50 for morphine 5 and for azidomorphine 0·025 mg kg^{-1}, i.p.
** Total dose was administered intraperitoneally in 7 gradually increasing doses over a 26 h period.

Tolerance and dependence

Table 4 compares the physical dependence capacity of morphine and azidomorphine in mice. The total dose of each analgesic was distributed in seven doses and injected intraperitoneally over 26 h. The difference between the two analgesics in this species is conspicuous. In mice pretreated with a total dose of 100 mg kg^{-1} of morphine, which is only 20 times the analgesic ED50 in mice, the average number of jumps during the 10 min after injection of 100 mg kg^{-1} of naloxone was 9·7. When the total dose of morphine was doubled, i.e. 40 times the analgesic ED50 dose (200 mg kg^{-1}) was administered, the maximum physical dependence developed (average jumps:

Table 5. *Development of tolerance to azidomorphine and morphine.*

Pretreatment: Drug	Pretreatment: Daily dose (mg kg^{-1} s.c.)	Pretreatment: Duration (weeks)	Drug tested*	Grade of tolerance (Hot plate) (DR**)
Azidomorphine	2 × 0·05	1	Azidomorphine	1·2
,,		5	,,	4·8
,,		7	,,	3·5
,,		12	,,	1·8
,,		17	,,	2·1
,,		17	Morphine	1 (ED50 = 3·8 mg kg^{-1})
Morphine	2 × 10	1	Morphine	2·0
,,		5	,,	5·2
,,		7	,,	5·6
,,		12	,,	5·2
,,		17	,,	5·3

* Testing: 16 h after the last injection of analgesic; drug administration 30 min before the test.
** DR = $\frac{\text{ED50 in chronically treated animals}}{\text{ED50 in controls}}$

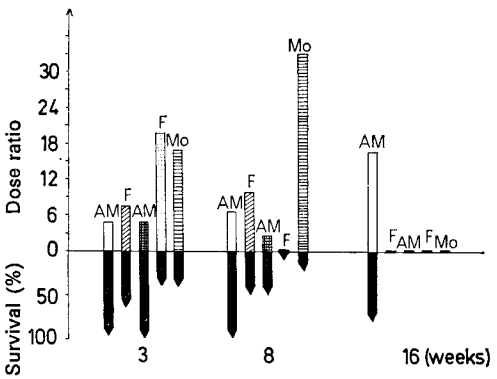


FIG. 4. Development of tolerance to azidomorphine (AM), morphine (Mo) and fentanyl (F) in rats treated with increasing doses. Grade of tolerance tested on the hot plate on the 3rd, 8th and 16th week, respectively. Schedule of drug administration (initial dose, mg kg^{-1}, in parentheses). Open columns azidomorphine (0·05): diagonally hatched columns fentanyl (0·05). Cross hatched columns, azidomorphine (2·5); dotted columns fentanyl (0·5); horizontally hatched columns, morphine (10). Increments of 0·025 mg kg^{-1} were given on every 2nd day (morphine 10 mg kg^{-1}). Each dose was administered subcutaneously twice a day to groups of 30 rats. Dose ratio = ED50 measured on treated/ED50 on control animals. ED50 values were calculated from dose-response curve.

46·4). On the other hand, mice treated with a total dose of 1 or 10 mg kg^{-1} of azidomorphine (i.e. 40 or 400 times the analgesic ED50 dose) did not develop physical dependence and even after treatment with a total dose of 2800 times the median analgesic dose, the average number of jumps precipitated by naloxone was only 7·4 (Table 4).

Table 5 shows the development of tolerance in rats after chronic administration of a constant daily dose of morphine and azidomorphine. A tolerance to azidomorphine is seen to develop between the 3rd and 7th week, but appears to be transitory since by the end of the 17th week the analgesic effect of azidomorphine practically returned to the initial level. In these animals, morphine appeared to be as effective (ED50 = 3·8 mg kg^{-1}) as in the controls (ED50 = 4·6 mg kg^{-1}). This fact also indicates that during azidomorphine treatment no tolerance developed to morphine. However, a tolerance was observed in morphine-treated animals.

Fig. 4 shows the development of tolerance in groups of animals treated with increasing doses of morphine, azidomorphine and fentanyl, respectively. Tolerance in the morphine-treated animals is of the highest grade, the dose ratio being as high as 35. Because of the significant toxicity of morphine and fentanyl, chronic experiments could not be made with these drugs, only the effects of azidomorphine could be followed up to the 16th week when 78% of animals were still alive.

Fig. 5 shows the severity of the abstinence syndrome precipitated in rats treated with rapidly increasing daily doses of morphine. In contrast to the morphine-treated animals nalorphine failed to precipitate abstinence symptoms in the group treated with fairly high doses of azidomorphine.

The same difference between azidomorphine and morphine was observed in monkeys treated with increasing doses of the drugs for 300 days. Withdrawal abstinence syndrome was evaluated first between the 55–59th day of the treatment. Table 6 shows the appearance of severe abstinence symptoms reaching their maximum on the 58th day. This state could be promptly relieved by the administration of

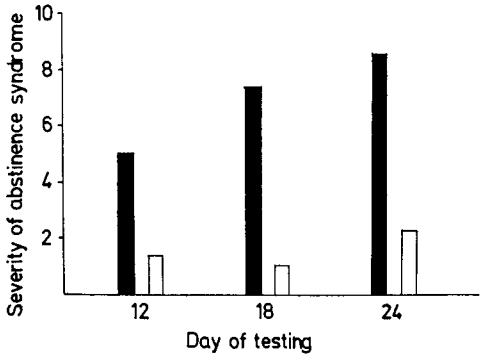


FIG. 5. Abstinence syndrome precipitated by nalorphine in rats treated chronically with rapidly increasing i.p. doses or morphine (solid columns) or azidomorphine (open columns). Treatment began with two daily doses of 20 mg kg^{-1} morphine, and 0·5 mg kg^{-1} azidomorphine, respectively. Daily doses increased by 20 mg kg^{-1} Mo and 0·45 mg kg^{-1} AM up to the 11th day, and from then on were kept constant.

morphine, but azidomorphine failed to antagonize the withdrawal syndrome in these animals. No sign of abstinence appeared in the group treated with azidomorphine. The starting dose was 1 mg kg^{-1} morphine and 0·015 mg kg^{-1} azidomorphine and was increased by about 0·5 and 0·009 mg each week, respectively. The second testing beginning at the 176th and the third on the 300th day of the treatment showed the same correlation.

DISCUSSION

The azido-derivative of morphine seems to possess a much more favourable spectrum of activity than any hitherto known major analgesic. Firstly, it has a much better

Table 6. *Evaluation of physical dependence liability on monkeys, treated with morphine.* Azidomorphine in doses from 0·015 mg kg^{-1}, s.c. increasing weekly to 2 × 0·4 mg kg^{-1} on the 300th day gave zero responses in animal on all days of testing (as for morphine).

	Day of testing	Suppressing: Drug	Suppressing: Dose mg kg^{-1}	No. animals tested	No of animals experiencing intensity of abstinence syndrome: Zero	Mild	Moderate	Severe
Morphine	55	—		6	—	2	4	—
	58	—		6	—	—	—	6
	59	MO	5	3	3	—	—	—
		AM	0·15	3	—	—	2	1
	175	—		6	—	—	5	—
	178	—		6	—	—	—	6
	179	MO	5	3	3	—	—	—
		AM	0·15	3			1	2
	300	—		6	—	—	—	6
	303	—		6	—	—	—	6
	304	MO	5	3	3	—	—	—
		AM	0·15	3	—	—	2	1

Withdrawal of either narcotic was between 55th and 59th, 175th and 179th and 300th and 304th days.

Morphine (MO) treatment: initial dose 1 mg kg^{-1} s.c., twice daily, and it was increased weekly, according to the sensitivity of the individuals. The final dose was 2 × 15 mg kg^{-1} at the 300th day.

median therapeutic index than morphine. Secondly, there is a remarkable dissociation between the analgesic potency and physical dependence in mice, rats and monkeys.

Our studies do not refute the conclusions drawn from recent investigations, namely, that structures exerting major analgesic effects set off certain, up to now unknown, biochemical processes resulting in the development of tolerance and dependence. Our experiments in the mouse jumping test clearly demonstrate that jumps were precipitated by naloxone in animals treated with very high doses of azidomorphine indicating a low physical dependence capacity of the compound. The same was demonstrated with pentazocine by Saelens & others (1971). In all probability there is no exception in this matter, all compounds capable of relieving severe pains are potentially producers of dependence.

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