An improved long-acting delivery system for narcotic antagonists

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Narcotic antagonists have proved potentially useful in combatting opiate addiction and prevention of relapse (Blumberg & Dayton, 1973; Martin, Jasinsky & Mansky, 1973). There is a need for long-acting delivery systems for pure narcotic antagonists with a long biological half life ($t_{\frac{1}{2}}$) (Willette, 1976). Biodegradable polylactic and lactic-glycolic acid composites have been used for cyclazocine and naltrexone (Woodland, Yolles & others, 1973; Yolles, Leafe & others, 1975; Schwope, Wise & Howes, 1976) and a non-biodegradable polymer for naloxone (Fishman, Hahn & others, 1975), also synthetic glutamic acid-leucine copolymers polyglycerides, insoluble salts and metal complexes of antagonists (Willette, 1976) have been employed. In general these vehicles have produced blockade of antinociceptive action of morphine for from 15 to 30 days. Woodland & others (1973) obtained $t_{\frac{1}{2}}$ values of 11 to 13 days on release of antagonist, a poor correlation between *in vitro* and *in vivo* data and an inflammatory process at the site of film implant; Yolles & others (1975) obtained effective blocking action to morphine in rats for 24 days ($t_{\frac{1}{2}}$ 22 days); Fishman & others (1975) observed the duration of antagonism for 22 days in rats and slight encapsulation of implant by surrounding tissue. The procedures involved in the preparation of the copolymers are complex and the reproducibility of polymerization conditions, use of pharmacologically suitable catalysts and overall tissue compatibility and toxicity of such copolymers require further attention. A recent report on the sustained release of a contraceptive steroid from fused cholesterol pellets (Gupta, 1977) prompted us to evaluate compressed pellets of cholesterol and glyceryltristearate as long-acting delivery systems for narcotic antagonists. We report here a promising delivery system for naltrexone which may have clinical usefulness in the treatment of narcotic dependence.

Cholesterol (360 mg), glyceryltristearate (40 mg) and naltrexone base (100 mg) were dissolved in 10 ml chloroform and the solution evaporated to dryness under vacuum in a Rotavapor and the residue further dried under vacuum overnight. The thoroughly mixed powder (50 mg) was compressed to a cylindrical pellet (54500 lb inch^{-2}; 375 50 MN m^{-2}), diameter 3 mm, length 6·35 ± 0·13 (s.e.m.) mm, weight 48·56 ± 0·77 (s.e.m.) mg, surface area 56·5 mm^2, volume 42·3 mm^3 in a Carver Laboratory Press (Fred Carver Inc. Summit N.J.). The pellets containing 10 mg naltrexone and the placebo pellets were implanted subcutaneously in the dorsal area behind the right hind limb of male Wistar rats, pushed away from the incision and the incision sutured. Groups of pellet-implanted rats (n = 5) were challenged each with a 10 mgl kg^{-1} (s.c.) dose of morphine at 15 days, 1, 1·5 and 2 months after implantation and the response latency (s) measured on a hot plate (55°), with a cut-off time of 30 s, before morphine injection and 0·5, 1, 1·5, 2 and 3 h after morphine injection. Control rats with placebo pellets were concurrently injected with morphine for comparison of their response latency with the naltrexone pellet-implanted animals. Data on the reaction times appear in Table 1. The response latencies in 30 day pellet-implanted animals at 0·5 to 2 h after the morphine dose were not significantly different from the reaction time before morphine injection by correlated *t*-test. At 1·5 and 2 months, the degree of analgesic blockade to this morphine dose was approximately 90 and 85% respectively. Three days following the removal of the naltrexone pellets, the reaction times observed between 0·5 to 3 h after the morphine dose were not significantly different from those in placebo-pelleted rats indicating that the implanted naltrexone pellets also blocked the development of tolerance to morphine. The results show that the delivery system produced complete and effective blockade of analgesia due to a 10 mg kg^{-1} (s.c.) dose of morphine in test animals for 1 month.

Radioactive pellets (10 mg naltrexone) were prepared using [15,16-^{3}H]naltrexone by the procedure described above and were implanted subcutaneously in a group of 7 rats. The excretion of radioactivity in urine collected in metabolism cages was measured every 24 h for 30 days by counting the radioactivity in an aliquot of urine in Bray's solution and correcting for quenching using [^{3}H]toluene as an internal standard. From a value of 2·5 ± 0·3% there was a steep fall to 0·8 ± 0·15% in three days, the values then declined slowly to 0·3 ±0·05% on day 30. The cumulative urinary excretions of radioactivity (mean ± s.e.m.) in 30 and 60 days were 17·7 ± 0·4 and 23·7 ± 0·9% respectively. In 90 days this excretion amounted to 25·7%. The pellets were removed 30, 60 and 90 days after implantation, dissolved in chloroform and radioactivity counted in an aliquot. The percent of radioactivity (mean ± s.e.m.) released from the implanted pellet in 30, 60 and 90 days were 55·8 ± 1·3, 68·8 ± 0·7 and 78·2% respectively. The excretion of radioactivity via faecal or other routes by subtraction therefore amounted to 38·14, 45·1 and 52·6% of implanted dose in 30, 60 and 90 days respectively. Thus the pellet gave a satisfactory release of naltrexone over an extended period of time.

These measurements of urinary radioactivity and of dose remaining at the site of implant at various times after implantation appear to us as valid parameters of naltrexone release *in vivo*. For a correlation of pharmaco-

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Table 1. *Response latencies*[1] *assessed on hot plate of rats implanted subcutaneously with 10 mg naltrexone pellets for various periods before and after the challenge dose (10 mg kg*$^{-1}$*, s.c.) of morphine.*

Test conditions	Reaction times after morphine injection					
	Before	0·5 h	1 h	1·5 h	2 h	3 h
30 days[2]	3·70 ± 0·44	4·72 ± 0·56 (NS)	5·82 ± 1·10 (NS)	4·44 ± 0·95 (NS)	5·58 ± 0·91 (NS)	—
45 days[3]	4·08 ± 0·27	5·88 ± 0·60*	7·44 ± 0·48*	5·92 ± 0·74**	6·08 ± 0·93**	—
60 days	3·36 ± 0·18	4·96 ± 0·39**	7·64 ± 1·12**	5·28 ± 0·90**	5·20 ± 0·17*	4·36 ± 0·45**
3 days after pellet removal[4]	2·92 ± 0·26	10·56 ± 2·77	25·76 ± 4·24	25·04 ± 4·96	20·92 ± 5·59	4·65 ± 0·50
Placebo pellet[4] (2 months)	5·55 ± 1·00	17·18 ± 4·65	20·75 ± 4·39	20·45 ± 4·46	18·15 ± 5·32	6·25 ± 2·08

1. Results are expressed as mean ± s.e.m. (s) from 5 rats. The temperature of hot plate was 55° and the criterion of reaction of the rat was licking of one paw or intensive jerking with lifting off or jumping of hind legs. The test was terminated if response latency exceeded 30 s (cut-off time). After being in place for 60 days, the pellets were removed and 3 days after removal the rats were each injected with a 10 mg kg^{-1}, subcutaneous dose of morphine.
2. NS denotes no significant differences in reaction times fromthat before mophine injection.
3. * Denotes significant difference at $P < 0.01$ and ** at $P < 0.05$ from that before morphine injection.
4. No significant difference in reaction times (0·5–3 h) of rats with placebo-pellets and those after pellet removal by *t*-test.

logically effective release rates and duration of narcotic antagonism, it would be desirable to determine the plasma or serum concentrations of naltrexone at various times after implantation in the same animal. Because of the partial exchange of tritium label with body water, Yolles & others (1975) concluded that urinary excretion of naltrexone was not a reliable measure of its excretion *in vivo*. These authors however utilized [^{3}H] randomly labelled material prepared by catalytic labelling of naltrexone in their study and this could explain the observed exchange with body water.

In our experiments neither deterioration of implant nor gross anatomic or histological changes at the site of implant occurred 3 months after implantation. No obvious side effects were observed in rats, which fed well and gained weight during treatment. The method thus has the merits of simplicity, non-toxicity, non-irritability, small size for ease of insertion and removal, bioabsorbability, absence of encapsulation by surrounding tissue and an extended period of drug release unaffected by body metabolism.

Notes added in proof

Pellets comprising naltrexone (30 mg), cholesterol (105 mg) and glyceryltristearate (15 mg), diameter 4·5 mm, length 9 mm, implanted subcutaneously in rats blocked the antinociceptive action of 10 mg kg^{-1} s.c. dose of morphine for 2–3 months.

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REFERENCES

BLUMBERG, H. & DAYTON, H. B. (1974). In: *Narcotic Antagonists*, Editors: M. C. Braude, Harris, L. S., May, E. L., Smith, J. P., Villarreal, J. E. Adv. Biochem. Psychopharmac., **8**, 33–43. New York: Raven Press.

FISHMAN, J., HAHN, E. F., NORTON, B. I., RONAI, A. & FOLDES, F. F. (1975). *Pharmacology*, **13**, 513–519.

GUPTA, G. (1977). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **36**, 997.

MARTIN, W. R., JASINSKY, D. R. & MANSKY, P. A. (1973). *Archs Gen. Psychiat.*, **28**, 784–791.

SCHWOPE, A. D., WISE, D. L. & HOWES, J. F. (1976). *Life Sci.*, **17**, 1877–1886.

WILLETTE, R. E. (1976). *Narcotic Antagonists: The search for long-acting preparations*, National Institute on Drug Abuse Research Monograph Series 4, Rockville, Maryland.

WOODLAND, J. H. R., YOLLES, S., BLAKE, D. A., HELRICH, M. & MEYER, F. J. (1973). *J. medl Chem.*, **16**, 897–901.

YOLLES, S., LEAFE, T. D., WOODLAND, J. H. R. & MEYER, F. J. (1975). *J. pharm. Sci.*, **64**, 348–349.