undertaken to determine the influence of a high concentration of lecithin on the irritative effect. Whether the improved rectal bioavailability of some drugs when using lecithin is related to the rectal mucosa damage is not clear, although van Hoogdalem et al (1990) in an evaluation of the topical effects of some absorption enhancing agents (octanoate, glyceryl-1-monodecanoate and decanoate) on the rectal mucosa, could not find a direct relationship between cefoxitin bioavailability and the extent of damage.

In summary, this study demonstrated that frequent application of triglyceride suppositories induced severe rectal mucosal damage resulting in erosion, ulceration and regeneration of the rectal mucosa; no hyperaemia was seen in the lecithin group while erosion, ulceration and regeneration occurred more frequently.

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The effects of a single dose of morphine on the concentration of substance P-like immunoreactivity in rat and guinea-pig brain

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Dependence in animals and man occurs following a single injection of morphine and other opioids, manifested as a withdrawal response on rapid removal of the opioid, or on administration of an opioid antagonist. Substance P is one of the neurotransmitters that plays a major role in the opioid withdrawal response in the isolated ileum (Chahl 1983) and central nervous system (CNS) (Johnston & Chahl 1991) of the guinea-pig. Therefore, it might be expected that substance P would be released from certain brain regions on opioid withdrawal. Contrary to expectation, however, it was found in in-vitro experiments that morphine itself produced release of substance P-like immunoreactivity (SP-LI) from thick saggittal slices of guinea-pig brain (Chahl 1990).

If morphine produced release of substance P in-vivo this might be reflected in a lowered tissue content. However, previous studies on rat brain have found that acute administration of morphine, 10 mg kg^{-1}, produced little or no effect on substance P levels, but that chronic administration produced increases in substance P levels (Bergstrom et al 1984). These observations in rat brain agree with the concept that opioids inhibit neurotransmitter release. In contrast, preliminary experiments on guinea-pig brain indicated that a single injection of morphine sulphate, reduced SP-LI levels (Chahl & Chahl 1989). To determine whether the effects of morphine were species-specific, we examined the effects of morphine and naloxone-induced morphine withdrawal on SP-LI concentrations in brain regions of rats and guinea-pigs.

Guinea-pigs of either sex, 410–660 g, and male rats, 160–280 g, were given either morphine sulphate (David Bull Laboratories, NSW, Australia), subcutaneously, or saline, and 2 h later morphine-treated animals were given either naloxone hydrochloride (Sigma Chemical Co. St Louis, MO), subcutaneously, or saline. Saline-treated animals were given either naloxone or a second injection of saline. Animals were killed by guillotine 30 min after the final injection. Brains were removed rapidly and dissected on an ice-cold glass plate into major regions using

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Table 1. Changes in substance P-like immunoreactivity (SP-LI) in guinea-pig and rat brain regions produced by morphine (15 mg kg^{-1}, s.c.) and naloxone (15 mg kg^{-1}, s.c.)-induced morphine withdrawal. Results are expressed as mean percentage differences from control ±s.e. (morphine control – saline/saline; morphine withdrawal control – saline/naloxone).

	Morphine (% of control)	Morphine withdrawal (% of control)
Cortex		
Guinea-pig	−4·6±1·8	−7·4±3·3
Rat	−17·0±4·4	−18·2±1·9
Striatum		
Guinea-pig	−17·2±6·7	−8·7±3·4
Rat	−13·7±3·0	−3·6±2·3
Diencephalon		
Guinea-pig	−23·7±2·5**	−12·1±3·3
Rat	−22·3±4·3*	−15·0±2·3
Midbrain		
Guinea-pig	−13·0±5·0	−5·3±4·9
Rat	−3·1±4·4	−16·2±3·2
Medulla/pons		
Guinea-pig	+1·2±3·6	+10·3±3·8
Rat	+14·8±6·1	+8·4±4·8
Spinal cord		
Guinea-pig	−10·7±3·0	+4·5±1·8
Rat	−6·5±3·1	−11·7±3·5

Asterisks indicate significant differences from control obtained in Bonferroni *t*-tests on SP-LI concentrations. **$0{\cdot}01 > P > 0{\cdot}001$; *$0{\cdot}05 > P > 0{\cdot}01$.

methods previously described (Glowinski & Iversen 1966). Tissues were frozen immediately in liquid nitrogen, weighed, and stored at −80°C until analysis. Tissues were extracted in both water and acetic acid according to the method of Lindefors et al (1986). Tissues were homogenized in 10 vol water, boiled for 10 min and centrifuged at 760 *g* for 10 min. The pellets were extracted with 10 vol 1 M acetic acid, boiled for 10 min and centrifuged. The water and acetic acid extracts were combined. The SP-LI contents of the extracts were measured using SP radioimmunoassay kits from Incstar (Stillwater, MN). Although the SP-LI cannot be identified with certainty, cross reaction of the Incstar SP antibody with other tachykinins is unlikely (Naukam et al 1990).

Following morphine injection, rats and guinea-pigs exhibited little spontaneous activity. Guinea-pigs, like man, were sedated by morphine but did not lose consciousness. Rats, which are nocturnal, were usually asleep before the experiment. After morphine injection they appeared alert with eyes wide open. Guinea-pigs given naloxone 2 h after morphine exhibited the typical withdrawal response for this species, which consisted of a marked increase in locomotor activity and behavioural signs such as digging, rearing and grooming. Rats did not exhibit these behaviours on naloxone-induced withdrawal following a single dose of morphine, but instead showed piloerection and subtle signs of agitation. Morphine produced significant reductions in the level of SP-LI compared with saline treatment only in the diencephalon of both species (Table 1). Naloxone-induced morphine withdrawal did not produce any significant effect on SP-LI levels compared with control animals given naloxone. The finding that morphine reduced SP-LI concentrations in the diencephalon of guinea-pig and rat brain, supports the proposal that acute morphine administration releases substance P in the CNS in-vivo as it has been found to do in-vitro (Chahl 1990). It is noteworthy that the hypothalamus has been identified as one of the regions which is strongly associated with opiate reinforcement and reward (Watson et al 1989).

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