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Letters to the Editor

Plasma levels of opioid material in man following sublingual and intravenous administration of buprenorphine: exogenous/endogenous opioid interaction?

J. E. OLLEY, G. K. L. TIONG *Department of Pharmacology, Monash University, Clayton 3168, Victoria, Australia*

The synthetic opioid buprenorphine has been reported to be an effective analgesic when given intravenously (Bartlett et al 1980) or sublingually (Bullingham et al 1982). Pharmacokinetic data on drug levels in plasma were previously gathered using radioimmunoassay (RIA) (Bartlett et al 1980) or radioreceptor assay (RRA) (Villiger et al 1981; Olley et al 1986). Recently, we (Tiong & Olley 1987) have developed an alternative to the RIA, the enzyme-linked immunoassay (EIA). This study aims to measure drug levels in plasma using both the RRA and the EIA. Plasma samples from 10 healthy volunteers were collected immediately before and then for 24 h after a single dose of buprenorphine, 0·4 mg i.v. or 0·8 mg s.l. Buprenorphine-like material was extracted from the plasma after storage at −20°C and assayed by RRA. 12 months later, the 0–4 h plasma samples of four subjects were assayed by EIA. Fig. 1a, b shows the buprenorphine-like activity detected in the plasma of the four subjects, detected using RRA and EIA, after i.v. and s.l. administration, respectively.

Whilst the use of either method of assay confirmed the salient features of each route of administration (Bullingham et al 1982; Olley et al 1986), there were interesting discrepancies. Plasma levels determined by EIA, although lower, were not always parallel to that determined by RRA, the greatest differences occurring in the pre-dose, the 5–90 min s.l. and 2–4 h i.v. samples. Thus differences between these two assays may not only be attributable to degradation during the storage period (as would be indicated by parallel shifts), but may reflect a variable endogenous opioid component which is recognized by RRA but not EIA.

Evidence in the clinical literature suggests that circulating β-endorphin can be rapidly depressed by morphine (Reid et al 1981; Abboud et al 1984) and this is consistent with animal data concerning morphine-induced suppression of methionine enkephalin release (Jhamandas et al 1984; Elsworth et al 1986). Furthermore, Marshall et al (1985) investigated the effect of an intravenous infusion of morphine to maintain analgesia. They noted greater morphine need in the group given the initial infusion treatment and considered the implications of these observations with respect to tolerance and endogenous opioid activity.

The preliminary data presented here suggest that another opioid, buprenorphine, may also modulate endogenous opioid levels in the plasma and that the rate of access to the nervous system may differentially modify the pattern of activity of endogenous opioid systems. Since disturbance of these may affect many physiological functions (Akil et al 1984) as well as being associated with opioid tolerance and dependence, further critical study of exogenous/endogenous opioid interaction is needed to optimize the clinical use of opioids and to avoid undue perturbation of endogenous opioid systems.

Correspondence to: G. K. L. Tiong, Dept of Pharmacology, Monash University, Clayton 3168, Victoria, Australia.

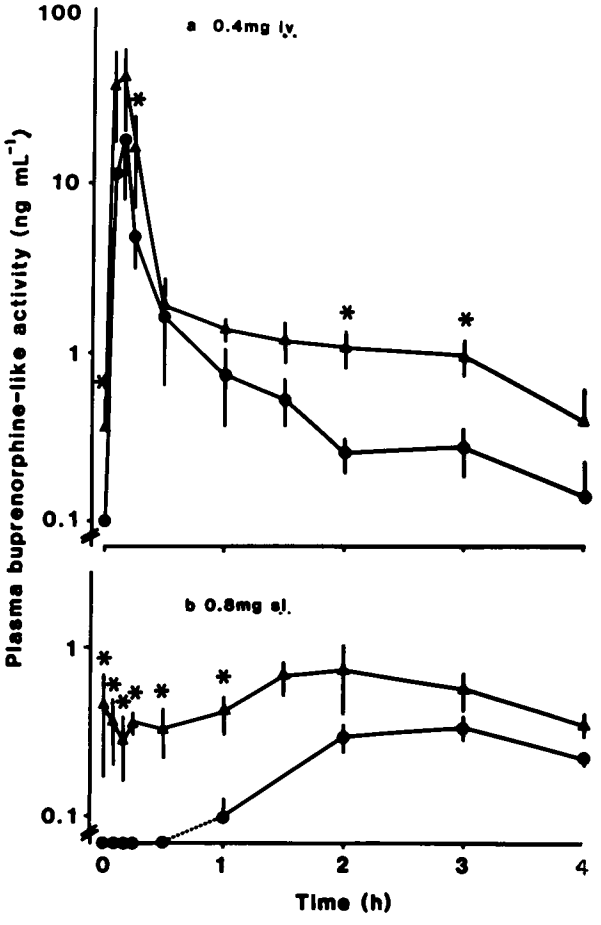

FIG. 1. Plasma levels of buprenorphine-like material in man (n = 4) following (a) i.v. administration and (b) s.l. administration when estimated using RRA (▲) and EIA (●). Vertical bars indicate s.e.m. * $P < 0.05$, Mann-Whitney U test.

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Indomethacin and cartilage breakdown

F. M. DESA, C. L. CHANDER, D. W. HOWAT, A. R. MOORE, D. A. WILLOUGHBY, *Department of Experimental Pathology, St Bartholomew's Hospital Medical College, Charterhouse Square, London EC1M 6BQ, UK*

We have previously shown that indomethacin will accelerate rat femoral head cartilage (FHC) breakdown when implanted subcutaneously in rats in juxtaposition to granulation tissue (De Brito et al 1987; Desa et al 1988). This has recently been confirmed following FHC implantation in mouse air pouches (Bottomley et al 1988) and antigen arthritis in rabbits (Pettipher et al 1988).

We have now shown that indomethacin fails to affect native cartilage in non-inflamed, load bearing joints following daily treatment for 14 days with 1–3 mg kg^{-1} indomethacin orally (control proteoglycan 395 $\mu g \pm 20$ s.e.m; indomethacin treated 405 $\mu g \pm 18$ s.e.m).

To determine the possible effects of mediators, in particular PGE_2, we have now performed some in-vitro experiments in which rat FHC was either cultured with recombinant IL-1α (rIL-1α) or indomethacin. These both failed to lower glycosaminoglycan (GAG) content of the cartilage. However, the level of PGE_2 released into the medium was low in the indomethacin group (0·63 ng mL^{-1}) and high in the rIL-1α group (5·45 ng mL^{-1}).

Table 1. The GAG content of rat femoral head cartilage measured according to Farndale et al (1982) and PGE_2 content of the medium measured by radioimmunoassay according to Salmon (1978). The culture conditions were as described by Desa et al (1988). All assays were performed after 1 week of culture.

Experimental group	n	Proteoglycan estimation (GAG content) μg (mean ± s.e.m.)	PGE_2 concentration ng mL^{-1} (mean ± s.e.m.)
FHC + medium (control)	6	252 ± 13	2·68 ± 0·73
FHC + rIL-1α (1300 units mL^{-1})	6	215 ± 19	5·45 ± 0·33**
FHC + indomethacin (100 μM)	5	214 ± 28	0·633 ± 0·06*
FHC + indomethacin (100 μM) + rIL-1α (1300 units mL)	6	152 ± 11*	0·80 ± 0·04*

*$P < 0·05$. **$P < 0·01$ (Student's t-test)

Correspondence to: D. A. Willoughby, Dept of Experimental Pathology, St Bartholomew's Hospital Medical College, Charterhouse Square, London EC1M 6BQ, U.K.

When cartilage was cultured with a mixture of rIL-1α plus indomethacin there was a significant loss of GAGs ($P < 0·05$) from the FHC's but a low level of PGE_2 (0·8 ng mL^{-1}) released into the medium. The lack of correlation between PGE_2 and GAG levels would seem to imply that it is unlikely that PGE_2 is involved in the breakdown of cartilage in this system.

In view of our previous findings that exudative inflammation will protect implanted cartilage from breakdown (Sedgwick et al 1985) it is suggested that those often used clinical assessments, of antirheumatics, that depend on heat, redness and swelling, may be misleading. Therefore alleviation of these cardinal signs of acute inflammation which indicate symptomatic relief, may under certain conditions be accelerating the underlying chronic pathological processes.

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