CORRESPONDENCE

THE PARADOX OF NALOXONE

Sir,—In their recent editorial Smith and Pinnock (1985) mentioned the fact that, although naloxone has been traditionally regarded as a pure opioid antagonist without agonist activity, evidence has accumulated that this may not be so. Later in the editorial, they opine that these apparently paradoxical actions of naloxone have now become explicable on the basis of the endogenous opioid peptide system—although some of its actions await clarification. However, the only theoretical explanation offered in the article for these effects is the differential sensitivity of the various opioid receptors to naloxone, with the latter being more active at mu than at delta and kappa sites. In view of the dearth of references given to this, possibly most important, paradoxical effect of naloxone we would like to refer to some of our own work on this topic.

To our knowledge we were the first to publish specifically on this paradoxical effect in human subjects in which naloxone was shown to both inhibit and enhance nitrous oxide analgesia in different subjects (Gillman, Kok and Lichtigfeld, 1980; Gillman and Lichtigfeld, 1981). In these papers we explained this unexpected analgesic effect of naloxone in terms of the existence of two opposing opioid systems, one analgesic and the other hyperalgesic—each having differential sensitivities to naloxone. Before our work Lasagna (1965) had noted an analgesic effect of naloxone at low doses, but did not investigate this observation further, most probably because it predated the discovery of the endogenous opioid system.

We have expanded our understanding of this phenomenon in a paper published recently (Gillman and Lichtigfeld, 1985) in which a great deal of independent confirmatory evidence is provided for the presence of two opposing opioid systems involved in pain processing, one being analgesic and the other hyperalgesic. Anatomical evidence for the hyperalgesic system postulated by us has been provided by Wu and colleagues (1983). Furthermore, these two systems may well play a part in other physiological processes and disease states, viz. cardiovascular homeostasis (Petty and de Jong, 1983), addiction (Gillman and Lichtigfeld, 1984), feeding behaviour (Gillman and Lichtigfeld, 1986), sexual behaviour (Gillman and Lichtigfeld, 1983) and ictal phenomena (Urca, Yitzhaky and Frenk, 1981).

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REFERENCES


NALOXONE — FRIEND OR FOE?

Sir,—Naloxone has attracted much recent attention because of its ability to produce arousal in non-opioid induced coma states. The arousal response may be so extreme as to produce many untoward effects and it has been suggested that naloxone should be used with caution (Smith and Pinnock, 1985). I would like to propose another reason for care in the use of naloxone as illustrated by a recent patient.

A 63-year-old man (ASA Class II) underwent surgery for recurrent squamous cell carcinoma of the nasal septum and ethmoid sinus. During surgery the brain was inadvertently entered, but the trauma was considered minor and the patient remained stable, subsequently to be transferred to the recovery room. He was noted to be drowsy, but otherwise his observations were normal. After 2.5 h in recovery he was still drowsy and so naloxone was administered to antagonize the narcotic which had been given during the operation. The patient responded immediately, became alert and started talking. The medical staff present all interpreted this as substantiating their diagnosis of narcotic “overdose” and left instructions for the resident staff to give further doses of naloxone as required. He received two further doses of naloxone which did not improve his condition markedly but, since his vital signs remained stable, no further action was taken until 7 h after his arrival in the recovery room. At this time a full neurological examination was undertaken because of his persisting somnolence. The CT scan revealed a subarachnoid haemorrhage with intraparenchymal blood under the Sylvian fissure, and blood in the ventricles with hydrocephalus. He was managed conservatively and his mental status returned to normal by the 2nd day after operation.

It is possible that, in this patient, the arousal response produced by the naloxone was mediated by improved cerebral blood flow to ischaemic brain rather than by opioid