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A comparison of the effects of fentanyl and alfentanil on the sleeping times of the intravenous induction agents

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The effect of increasing doses of fentanyl and alfentanil administered before four intravenous induction agents (thiopentone, methohexitone, Althesin and etomidate) on the sleeping time were studied in mice. A biphasic pattern of sleeping time was noted with the more rapidly metabolized and eliminated compounds. Possible explanations are discussed.

The supplementation of the intravenous induction agents with an opiate is a commonly used anaesthetic technique to ensure a smoother induction and peroperative analgesia (Kay & Stephenson 1980).

Fentanyl and its shorter acting derivatives such as alfentanil may be the drugs of choice since recovery times are not significantly impaired. Alfentanil has even been suggested to have an analeptic action (Sinclair & Cooper 1983) although subsequent studies have failed to confirm this (Cooper et al 1983). Clinical studies comparing the actions of fentanyl and alfentanil with one or two induction agents have shown varying results in both the amount of induction agent necessary for the initial sleep dose and for the maintenance of anaesthesia. Craig et al (1982) showed a significant decrease in the dose of Althesin (alphaxalone-alphadolone acetate) and methohexitone required when fentanyl was used as an adjuvant with no change in recovery time when compared with controls. Other studies have shown that less methohexitone was required when alfentanil was used as an adjuvant when compared with fentanyl, although the non comparable analgesic doses may have influenced these finds and statistical significance was not reached (Hull & Jacobson 1983).

This study aimed to examine (in the experimental animal) the effects of increasing concentrations of fentanyl and alfentanil on the duration of sleep and the dose required to produce this by four induction agents—thiopentone and methohexitone, which are mainly redistributed, and the more rapidly cleared and metabolized drugs Althesin and etomidate (Dundee & Wyant 1974). Since in this preliminary study it was intended to use a large range of doses, mice were chosen.

Methods

Female Manchester strain white mice, 25–35 g, were used. Preliminary experiments determined the dose of induction agent necessary to produce sleep. This was achieved by slow infusion (0·1 ml min^{-1}) of dilute mixtures via a tail vein until relaxation was observed then the injection was stopped and the dose required (mg kg^{-1}) was calculated for each induction agent (Table 1). Faster speeds at injection caused occasional fatalities. The mice were removed from the restrainer and placed on their backs in high sided cages to prevent draughts. They were closely observed until they spontaneously righted themselves. This was taken as the sleep time. The order of administration of induction agents was randomized to account for diurnal variations in sleeping times.

The relative analgesic potency of alfentanil and fentanyl in the strain of mice used was determined using the hot plate reaction time test (Bousfield & Rees 1969). Reaction times were tested every 2 min after opioid injection until no further increases were recorded.

Fentanyl (0·0125–1·0 mg kg^{-1}), alfentanil (0·05–1·5 mg kg^{-1}), or saline (NaCl 0·9%) was injected via the intraperitoneal route. All doses were diluted so that equal volumes on a 10 ml kg^{-1} basis could be given. Thus, it was possible to administer the opioid or saline control on a blind basis. After 15 min, one of the induction agents was given via a tail vein using the technique described above until sleep was achieved and the dose required recorded. Similar results were produced with 5 and 10 min pretreatment with the opioids. Twelve mice were used for each experiment and the doses of induction agent required in test and control mice were compared using Student's *t*-test. To accommodate the week to week variation in sleeping time that occurs in mice, the concurrent saline control sleeping time was subtracted from the test groups when the code had been broken to give a difference in sleep time which was plotted graphically against the opioid concentration. Significance from concurrent controls was assessed using the Mann Whitney U-test (2-tailed).

Results

The mean sleeping time for each of the induction agents in the absence of opioids is shown in Table 1. In general mice slept longer with Althesin than with the other agents. There was no significant difference in the doses of induction agents required for sleep in the opioid- and saline-treated mice. For example, the dose of Althesin necessary to induce sleep in mice pretreated with alfentanil 0·8 mg kg^{-1} was 6·0 (range 5·4–6·5) mg total

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Table 1. Dose and sleeping time for four induction agents in mice in the absence of opioids.

Induction agent	Dose mg kg^{-1} i.v. mean (range)	Dilution	Sleeping time (min mean with range)
Thiopentone Na	26·2 (20–30)	0·25% soln	2·77 (1·86–3·87) n = 84
Methohexitone Na	7·9 (3·5–10)	0·1% soln	1·56 (1·36–1·99) n = 84
Etomidate	3·13 (3–4)	0·05% soln	2·52 (1·83–3·36) n = 96
Althesin	5·62 (5–9)	0·01% soln	4·10 (2·5–7·9) n = 84

steroid (n = 12). Late, and usually fatal, respiratory depression occurred 3–5 min after induction when fentanyl 1 mg kg^{-1} and alfentanil 1·5 mg kg^{-1} were given before thiopentone and Althesin. These results have not been included in the figures as too few survived to be analysed statistically. No deaths occurred with lower doses of the two opioids in combination with thiopentone and Althesin.

Both fentanyl and alfentanil produced qualitatively similar effects on the sleeping time induced by the induction agents. The pattern of change in sleeping time differed with each of the four induction agents. The opioids produced biphasic changes in the sleeping times produced by Althesin and etomidate (Fig. 1c,d). This was less obvious with methohexitone and hardly discernable with thiopentone (Fig. 1a,b).

Since the biphasic effects of the opioids were unexpected, peak and trough doses of the opioids were repeated using the same protocol as described previously. Quantitatively similar results were obtained. For example on the first occasion the mean increase in sleeping time ± s.e.m. after etomidate for mice given 0·5 mg kg^{-1} alfentanil was 3·2 ± 1·3 min and for mice given 1 mg kg^{-1} alfentanil, 1·1 ± 0·6 min. On the second occasion those values were 3·5 ± 0·5 min and 0·7 ± 0·6 min, respectively. The mean values from all 24 mice have been included in Fig. 1c and d.

Fentanyl and alfentanil produced a dose-dependent increase in hot plate reaction time (Fig. 2) over the dose range used to study interactions with the induction agents.

Discussion

The interaction between fentanyl and alfentanil on the one hand and the four intravenous anaesthetics on the other may be pharmacodynamic or pharmacokinetic. High doses of fentanyl and alfentanil are known to cause sedation although alfentanil is more likely to have this property than fentanyl in equianalgesic doses in man (De Castro 1977) and the rabbit (Brown et al 1980). In

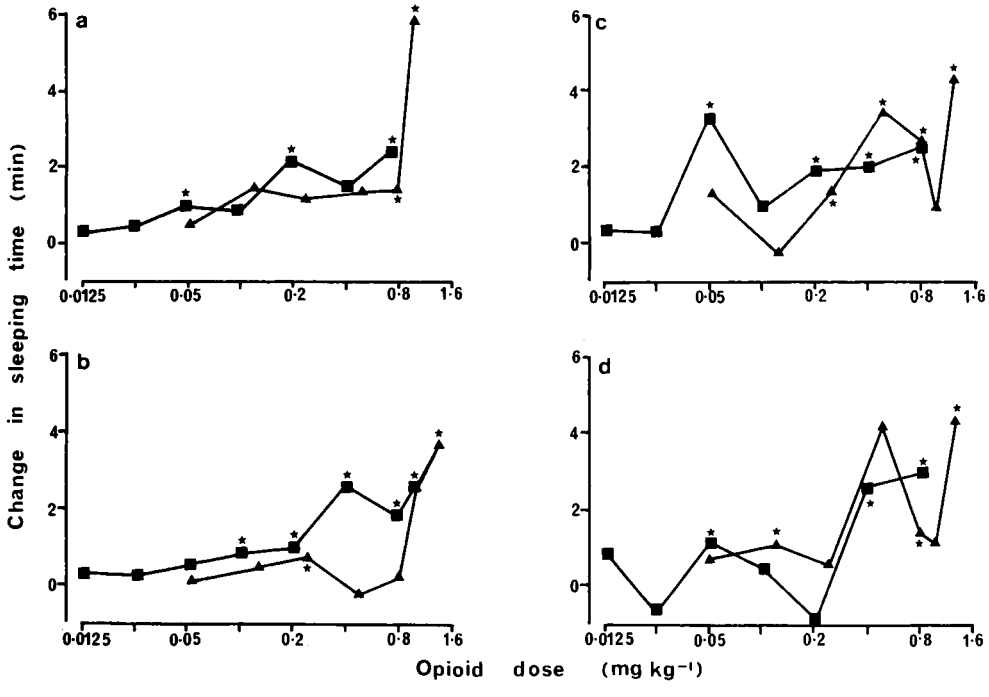

FIG. 1. Interactions of alfentanil (▲) and fentanyl (■) with the intravenous induction agents (a) thiopentone (b) methohexitone (c) etomidate and (d) Althesin. Results are mean change in sleeping time in opioid-treated mice from concurrently tested saline-pretreated mice (n = 12). *P < 0·05 Significantly different from concurrently tested saline-pretreated mice—Mann Whitney U-test.

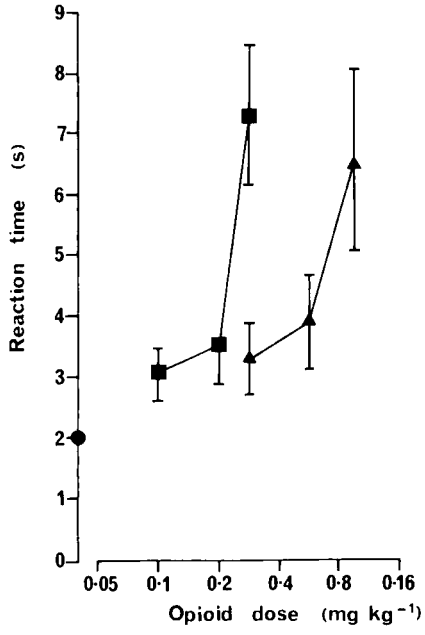

FIG. 2. Effects of fentanyl (■) and alfentanil (▲) on the hot plate reaction time of mice. Saline control values (●) are shown on the ordinate. Results are expressed as mean maximum response ± s.e.m. Maximum response to alfentanil occurred 2–4 min after injection whilst maximum responses to fentanyl occurred 6–10 min after injection.

this study, however, high doses of both fentanyl and alfentanil appeared to cause sedation in the mouse. Thus a summation of sedative properties of opioids and anaesthetics might be expected to cause a dose-dependent increase in sleeping time. This type of interaction was seen with fentanyl and alfentanil in combination with thiopentone and to a lesser extent with methohexitone. In combination with Althesin and etomidate moderate doses of alfentanil and fentanyl in mice failed to increase sleeping time whilst lower and high doses did increase sleeping time. There was no obvious excitatory effects of these moderate doses of opioids when given alone. An involvement of pharmacokinetic interactions is hinted at if the mechanisms of the recovery from the four anaesthetics is considered.

The four induction agents used vary in their pharmacokinetic properties. Thiopentone reaches maximum tissue concentration within 1 min of induction and undergoes rapid distribution. Subsequent metabolism is slow and recovery from a bolus dose of thiopentone is due to redistribution (Dundee & Wyant 1974). Methohexitone is also redistributed but metabolism plays a greater part in recovery than it does for thiopentone (Breimer 1976). Etomidate is hydrolysed by esters in the liver and plasma before elimination but recovery is due to both metabolism and redistribution. Althesin is rapidly eliminated, not redistributed (Ghonheim & Korttila 1977).

Thus the biphasic response to alfentanil and fentanyl is only seen with the anaesthetics in which biotransformation is important for recovery. No definitive evidence for a mechanism of the interactions observed has been obtained in this study but it would appear that the interaction observed depends both on the dose of opioid and the interacting anaesthetic at least in the mouse. If similar observations were applicable to man it might explain the variability in results obtained for interaction between alfentanil and various induction agents (Sinclair & Cooper 1983; Cooper et al 1983).

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