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Alfentanil-mediated analgesia during propofol injection: no evidence for a peripheral action

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Summary

We have investigated if alfentanil acts via peripheral opioid receptors to relieve the pain which occurs on injection of propofol. Thirty seconds before induction of anaesthesia and immediately after a tourniquet at 50 mm Hg greater than systolic pressure was inflated on the upper arm, patients were given either placebo ($n = 22$), alfentanil 1 mg ($n = 22$) or lignocaine 40 mg ($n = 22$) via an i.v. cannula in the dorsum of the hand. Pain during injection of propofol was assessed using a three-point verbal rating scale, recorded at 8-s intervals. We found a significant reduction in pain after lignocaine compared with the two other groups ($P < 0.001$), but there was no difference between the placebo and alfentanil groups. We conclude that alfentanil does not relieve pain on injection with propofol via an action on peripheral opioid receptors when alfentanil is limited to the forearm for 30 s before induction of anaesthesia. (*Br. J. Anaesth.* 1996; **77**: 162–164)

Key words

Anaesthetics i.v., propofol. Analgesics opioid, alfentanil. Receptors, opioid. Pain, injection.

Recent work suggests that opioid analgesia may be mediated, at least in part, via peripheral opioid receptors [1]. Prior administration of alfentanil is known to reduce the pain that occurs after an injection of propofol [2]. In a recent study alfentanil was given 15 s before propofol [3]. Significant analgesia was demonstrated approximately 30 s after administration of alfentanil. This rapid onset of analgesic effect is inconsistent with other pharmacodynamic data [2, 4] for alfentanil. This may be explained by alfentanil acting, at least partially, on peripheral opioid receptors. In this double-blind, placebo-controlled study, we have further investigated this phenomenon by pretreatment with alfentanil in the presence of a tourniquet. We also compared the efficacy of alfentanil with lignocaine, an agent which acts locally to prevent propofol-induced pain [5].

Patients and methods

After obtaining Ethics Committee approval and informed consent, we studied 66 patients. Patients were ASA I–II, aged 18–65 yr, undergoing elective day-case surgery and were unpremedicated. After transfer to the anaesthetic room, non-invasive monitoring was commenced and a 22-gauge i.v. cannula sited in the dorsum of the non-dominant hand. Patients were allocated randomly using a sealed envelope technique to one of three groups ($n = 22$ in each group): group 1 received normal saline, group 2 alfentanil 1 mg and group 3 lignocaine 40 mg. A tourniquet was applied to the non-dominant arm, the cuff inflated to 50 mm Hg greater than systolic arterial pressure and the pretreatment dose injected in a total volume of 2 ml. All solutions were prepared by the same investigator (I.W.) who did not assess pain. Thirty seconds after the pretreatment bolus, the tourniquet was deflated and propofol 10 mg ml^{-1} was infused at a rate of 1200 ml h^{-1} using a Graseby 3400 infusion pump. Patients were then asked by a blinded second investigator (K.G.), to assess any discomfort in the arm below the level of the tourniquet at 8-s intervals using a three-point verbal rating scale (none, mild, severe) until loss of consciousness. The time taken to induce anaesthesia, and the volume of propofol required, were noted.

Statistical analysis was by ANOVA and chi-square, as appropriate, with $P < 0.05$ as significant. Previous work has indicated that alfentanil reduces the pain of injection of propofol by at least 50 % [2]. On this basis 22 patients were needed in each group to confer a power of 0.9 at a P value of 0.05.

Results

The three groups were similar in age, weight and sex distribution, with no significant differences for duration of induction of anaesthesia. The dose of propofol given was significantly smaller in those who received alfentanil than in the two other groups (table 1).

Pain reported by patients in the three groups is shown in table 2. When considering the worst pain for each patient throughout the study, there was significantly less pain reported by patients who were given lignocaine before propofol compared with the two other groups ($P < 0.001$) (table 3). There was no difference in pain between patients who received alfentanil and placebo (table 3).

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Table 1 Patient data, volume of propofol given and time taken to induce anaesthesia (mean (SD or range) or number). The only significant difference between groups was the volume of propofol used in the alfentanil group (*$P < 0.05$)

	Saline group	Alfentanil group	Lignocaine group
Age (yr)	34.18 (17–55)	33.95 (18–52)	33.36 (23–46)
Sex (M : F)	1 : 19	1 : 19	2 : 18
Weight (kg)	61.53 (12.9)	65.60 (8.7)	64.10 (9.7)
Propofol (ml)	18.70 (2.2)	16.52 (2.3)*	18.90 (3.1)
Induction time (s)	50.10 (6.2)	45.68 (6.0)	50.90 (10.2)

Table 2 Number of patients who were asleep or reporting none, mild or severe pain at 8-s intervals during induction of anaesthesia with propofol. Each column shows the distribution of the 22 patients at each time

	Time (s)							
	8	16	24	32	40	48	56	64
Saline ($n = 22$)								
Asleep	0	0	0	0	2	11	20	22
None	13	8	7	8	8	6	1	0
Mild	7	8	8	7	7	1	0	0
Severe	2	6	7	7	5	4	1	0
Alfentanil ($n = 22$)								
Asleep	0	0	0	0	7	15	22	22
None	11	11	11	12	8	5	0	0
Mild	4	5	8	7	6	2	0	0
Severe	5	6	3	3	1	0	0	0
Lignocaine ($n = 22$)								
Asleep	0	0	0	0	4	9	18	22
None	22	22	21	21	16	11	3	0
Mild	0	0	1	1	2	2	1	0
Severe	0	0	0	0	0	0	0	0

Table 3 Worst pain reported by patients in each group after injection of propofol. Patients in the lignocaine group reported lest pain than the two other groups ($P < 0.001$)

	Saline group ($n = 22$)	Alfentanil group ($n = 22$)	Lignocaine group ($n = 22$)
None	7	11	20
Mild	7	4	2
Severe	8	7	0

Discussion

The use of propofol for induction of anaesthesia is common and has been shown to be associated with pain in up to 84 % of patients [3]. Many different factors have been associated with this phenomenon, including the temperature of the solution [6], size of the vein and speed of injection [7]. It has been shown that both lignocaine and alfentanil are effective in reducing the discomfort caused by propofol [2, 5] and that lignocaine has its maximum effect when given as pretreatment with a venous tourniquet occluding the proximal part of the arm [8].

Fletcher, Seavell and Bowen gave a bolus of alfentanil 15 s before induction of anaesthesia with propofol and showed a reduction in pain from 84 % to 36 % [3]. This difference started to become apparent 31 s after alfentanil has been given. This rapid onset of action conflicts with the published pharmacodynamic data of a half-time for access of alfentanil to the central biophase of 54 s [4] and a peak onset time of 90–120 s [2]. We designed this study to see if this discrepancy might be explained in part by alfentanil acting via peripheral opioid receptors to relieve the pain on injection of propofol. Peripheral opioid receptors have been identified in both animals and humans [9, 10]. Their physiological function is unclear, although it has been suggested that they may play a role in the inflammatory response [1] and recent work has suggested that both morphine and pethidine may relieve pain via peripheral opioid receptors when injected into the knee after arthroscopy [11].

In this study we were careful to control for cannula size and the temperature and rate of infusion of propofol. We included a group pretreated with lignocaine and a placebo group as we wished to compare the effects of an agent which is known to act locally, with any peripheral effect of alfentanil.

The incidence of pain in our saline and lignocaine groups supports the findings of a previous study where a venous tourniquet was used [8]. The combination of a tourniquet with lignocaine renders this a highly effective method for relieving the pain of injection of propofol, as Mangar and Holak demonstrated in their work. In our study, two patients in the lignocaine group complained of mild pain in the upper arm at 40 s (table 2) and it may be that to totally prevent pain it is necessary to use a larger volume of injection.

The statistically significant finding of reduced dose of propofol in the alfentanil group compared with those who received saline and lignocaine was not unexpected as Wall and Zacharias demonstrated a similar finding in their study [2]. Although not statistically significant, seven patients being asleep at 40 s in the alfentanil group compared with four in the lignocaine group and two in the saline group at the same time, makes our results more difficult to interpret, however, there are several interesting observations. The worst pain reported by patients receiving alfentanil confined to the forearm using an arterial tourniquet was comparable with those who received saline. This contrasts with the finding that alfentanil used without a tourniquet does relieve propofol pain [2, 3], suggesting that alfentanil acts solely at central opioid receptors. Examining our results more closely (table 2), there may be a reduction in the incidence of pain in the alfentanil compared with the saline group from 24 s onwards, as there were four fewer patients with severe pain (four more with no pain) at both 24 and 32 s. However, if this was the result of a peripheral opioid effect, we would have expected to also detect a difference between groups at earlier times having already pretreated the forearm with alfentanil for 30 s.

There are no data to indicate the time for alfentanil to access a potential peripheral biophase. We accept that 30 s may be too short a time for alfentanil to achieve this. However, if a peripheral opioid action contributed to the analgesia observed by Fletcher, Seavell and Bowen at 30 s, we anticipated reproducing the effect by confining alfentanil to the arm

for this time before injection of propofol. Increasing tourniquet time results in greater discomfort in the patient's arm and ethical considerations limited us to this time period for our initial study. However, the rapid onset time of alfentanil found by Fletcher, Seavell and Bowen is inconsistent with known pharmacodynamic data, as stated above. One explanation could be that when given as a rapid bolus the half-time for access to the central biophase is actually less than 54 s, and with a relatively mild pain stimulus, lower concentrations of alfentanil are required at receptors to provide adequate analgesia. It is also possible that we have used an inappropriate opioid and further studies might examine the use of more potent or lipid soluble opioids.

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