Alcohol Consumption Alters the Pharmacodynamics of Alfentanil


Two groups of women, ASA physical status 1, undergoing surgery for primary breast cancer, were studied to assess the effect of alcohol intake on alfentanil pharmacodynamics. Patients in group 1 (n = 6) had an average daily consumption of 20–40 g alcohol. Patients in group 2 (n = 8) were life-long abstainers or drank only occasionally (<60 g per year). Anesthesia was induced and maintained with 66% N2O in O2 and alfentanil. Alfentanil was administered by a computer-controlled infusion pump. If during surgery the patient exhibited somatic, hemodynamic, or other autonomic signs of inadequate anesthesia (response), the target alfentanil plasma concentration was increased by 50–100 ng/ml. If there was no response during a 15-min period, the target concentration was decreased by 50–100 ng/ml. Arterial blood samples were taken before any change of the target concentration, 4 min after a new predicted target concentration was achieved, and at extubation. Plasma concentrations were determined by capillary gas chromatography. Alfentanil protein binding was measured by equilibrium dialysis. Plasma alfentanil concentration–effect data were analyzed by nonlinear regression, where effect was either response or no response to surgical stimuli. The average total alfentanil requirement was significantly (P < 0.005) higher in group 1 (3.7 ± 1.2 µg·kg⁻¹·min⁻¹) than in group 2 (1.9 ± 0.4 µg·kg⁻¹·min⁻¹). The average Cp₅₀ (the plasma concentration for which the probability of no response during surgery is 50%) was significantly (P < 0.001) higher in group 1 (522 ± 104 ng/ml) than in group 2 (208 ± 26 ng/ml). The average plasma concentration at extubation in the patients who did not need naloxone was significantly (P < 0.005) higher in group 1 (372 ± 114 ng/ml, n = 5) than in group 2 (176 ± 39 ng/ml, n = 6). There was no difference in the plasma protein binding of alfentanil between the groups. The results of this study indicate that regular alcohol consumption leads to pharmacodynamic tolerance to alfentanil. (Key words: Analgesics: alfentanil; opioids. Anesthetics, intravenous: alfentanil. Pharmacodynamics: alcohol consumption; alfentanil. Tolerance: alfentanil; ethanol; opioids.)

ETHANOL (ethyl alcohol) is probably the most widely used drug in the world. Chronic alcoholics have an increased fentanyl requirement during anesthesia, which could be caused by an alteration in the pharmacokinetics of fentanyl. An alternative explanation for the increased fentanyl requirement could be a reduced sensitivity to its CNS effects. Pharmacodynamic cross-tolerance may develop to the effects of pharmacologically related drugs. Ethanol and opioids have several effects in common, e.g., euphoria, analgesia, respiratory depression, cutaneous vasodilation, addiction, and the development of tolerance. Naloxone, a specific opioid antagonist, can reverse ethanol-induced coma and prevents the impairment of psychomotor performance induced by low levels of blood ethanol. This suggests that the effects of ethanol are at least in part mediated by opioid receptors.

We studied the effects of alcohol consumption on the pharmacodynamics of alfentanil. Alfentanil’s rapid blood–brain equilibration facilitates assessment of pharmacodynamics during anesthesia and surgery.

Materials and Methods

After approval by the local medical ethics committee and obtaining informed consent, two groups of white female patients undergoing surgery for primary breast cancer were studied. None of the patients was receiving medication or had a history of drug abuse. Patients who smoked more than 10 cigarettes per day were excluded from the study. Alcohol consumption was determined by detailed independent interviewing by two experienced physicians, not otherwise involved in the study. Patients in group 1 (n = 6) had an average alcohol consumption of the equivalent of 20–40 g per day. One glass (100 ml) of wine (12 vol%), one glass (250 ml) of beer (5 vol%), or one glass (30 ml) of brandy (40 vol%) contains approximately 10 g ethanol. Those in group 2 (n = 8) were life-long abstainers or drank alcohol only on rare occasions (<60 g per year). Patients whose alcohol consumption in the 2 weeks before surgery was not typical of that in the previous year were excluded from the study. Patients had their last consumption of alcohol on the day before admission to the hospital, which is 1 day before the operation. None of the patients had delirium tremens, signs of alcohol withdrawal, or clinical evidence of liver disease. Routine liver function tests, serum bilirubin, alkaline phosphatase, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and lactic dehydrogenase, were all in the normal range.

Alfentanil was administered by a computer-controlled infusion pump (TIAC, Titration of Intravenous Agents by Computer; Janssen Scientific Instruments, Janssen Pharmaceuticals, Belgium). The computer was supplied with pharmacokinetic data reported by Schütter and Stoeckel. The target plasma concentration of alfentanil can be rapidly attained, maintained, or altered. If the

* Staff Anesthesiologist.
† Professor of Anesthesiology.
‡ Laboratory Technician.
§ Director of the Anesthesia Research Laboratory.

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Address reprint requests to Dr. Lemmens: Department of Anesthesiology, University Hospital, P.O. Box 9600, 2300 RC Leiden, The Netherlands.
target plasma concentration is increased, the new set point is theoretically achieved within 6 s. When the target concentration is decreased, the time to attain the new set point is largely dependent upon the pharmacokinetics and the dose history of the drug.

Preanesthetic medication included oral temazepam 20 mg 1 h and atropine 0.5 mg im 0.5 h before surgery. On arrival in the operating room ECG electrodes were placed. A 20-G cannula was inserted in a radial artery for continuous measurement of blood pressure and collection of blood samples. Before induction of anesthesia, 300–500 ml of 0.9% sodium chloride was infused. Pancuronium, 0.02 mg/kg, was given to prevent muscle rigidity. After the patients breathed oxygen for 3 min, the fresh gas flow was changed from 100% oxygen to 66% nitrous oxide in oxygen. Simultaneously, an infusion of alfentanil was started. The target alfentanil plasma concentration for induction of anesthesia was 350 ng/ml to be achieved in 2 min. When consciousness was lost succinylcholine, 1 mg/kg, was given, and the trachea was intubated. After intubation the target alfentanil plasma concentration was lowered to 200 ng/ml. Ventilation was adjusted to maintain end-tidal carbon dioxide concentration between 4 and 5 vol%.

If during surgery the patient showed signs of inadequate anesthesia, the target alfentanil plasma concentration was increased by 50–100 ng/ml. If necessary, this was repeated every 5 min. Inadequate anesthesia was defined by the following criteria:

1. Increase in systolic blood pressure by more than 15 mmHg above normal for that patient. Normal was defined as the lowest pressure measured in the time from admission to hospital until just before premedication.

2. A heart rate greater than 90 beats/min in the absence of hypovolemia.

3. Other autonomic signs, such as sweating, flushing, or lacrimation.

4. Somatic responses, such as movements, swallowing, coughing, grimacing, or eye movement.

If no response occurred during a 15-min period, the target plasma concentration was decreased by 50 ng/ml. If, after decreasing by 50 ng/ml, no response occurred in the following 15 min, the target plasma concentration was again decreased, this time by 100 ng/ml. To facilitate the identification of an increase in systolic blood pressure or heart rate, these parameters were continuously displayed and recorded. To facilitate the identification of a somatic response, minimal doses of pancuronium were given. Neuromuscular blockade was monitored using the train-of-four method, by percutaneous stimulation of the facial nerve (Myotest, Odense, Denmark).

During the study each patient was observed by two persons: a resident anesthesiologist, who was blinded to the drinking history of the patient, and an anesthesiologist (H.J.M.L.) who was not blinded to the drinking history of the patient. Both persons, who were completely familiar with the definition of inadequate anesthesia as used in this study, looked continuously for a response. If a response was detected, it was only accepted if verified by both observers. To avoid hypovolemia, fluid balance was evaluated at least every 15 min and maintained positive. Intravenous fluids consisted of 0.9% sodium chloride.

At the end of surgery nitrous oxide was discontinued, and residual neuromuscular blockade was antagonized if indicated with atropine, 0.5 mg, and neostigmine, 1 mg. The trachea was extubated after the patient recovered consciousness and when ventilation was adequate without stimulation (frequency > 10 breaths/min, end-tidal CO₂ < 6.5 vol%, tidal volume > 7 ml/kg). If 10 min after discontinuation of nitrous oxide ventilation was not adequate, naloxone 0.04 mg iv, was given every 3 min until adequate ventilation occurred without verbal encouragement. Patients of both groups were studied in a mixed sequence.

BLOOD SAMPLING AND ASSAYS

Before starting the administration of alfentanil an arterial blood sample was withdrawn for determination of alfentanil plasma protein binding. Additional arterial blood samples for the determination of alfentanil plasma concentrations were collected before any change in the target alfentanil plasma concentration and 4 and 15 min after a predicted target plasma concentration was achieved. In patients in whom ventilation recovered spontaneously, an additional blood sample was taken immediately before extubation. Arterial blood samples for the determination of PaCO₂ were taken 15, 30, and 60 min after extubation.

The plasma protein binding of alfentanil was determined by equilibrium dialysis with a Dianorm® dialysis system, equipped with 20 Teflon dialysis cells (Diachema, Rüschlikon, Switzerland). The cell membranes had a molecular weight cut-off of 10,000 daltons. One-milliliter plasma samples were spiked with 500 ng of alfentanil and dialysed against 2 ml of an isotonic (µ = 0.345 m, pH = 7.4) phosphate buffer solution, consisting of Na₂HPO₄ (107 mm) and KH₂PO₄ (24 mm). The dialysis was carried out in a thermostated water bath at 37° C for 4 h at 20 rpm. Under these conditions binding of alfentanil to the membrane or the cell walls was minimal (<5%). The non-specific binding was determined from the difference between the amount of drug added to the plasma before dialysis and the amount recovered from the buffer solution and plasma after dialysis.

Free fractions of alfentanil were determined from the concentrations Cp of alfentanil in plasma before dialysis.
and the concentration $C_d$ in dialysate after dialysis using the following equation (after Tozer et al.\textsuperscript{13}):

$$I_u = \frac{C_d}{C_p - 2C_d}$$

Concentrations of alfentanil in plasma and dialysate were determined by capillary gas chromatography. R 38527 (Janssen Pharmaceutica, Beerse, Belgium) as internal standard was added to 0.2 ml plasma or 0.5 ml dialysate and, after mixing, the sample was extracted for 30 s with 5 ml of redistilled reagent grade n-pentane (Merck, Darmstadt, FRG) on a whirl mixer. After centrifugation the organic phase was transferred to a conical centrifuge tube and evaporated to dryness in a stream of dry nitrogen on a water bath at 40°C. The residue was dissolved in 50–100 µl analytic grade absolute ethanol (Merck, Darmstadt, FRG), and 1 µl was introduced into the gas chromatograph via a falling needle solid injection system (Chrompack, Middelburg, The Netherlands).

Analyses were carried out with a Hewlett Packard 5890A gas chromatograph, equipped with a nitrogen detector and a capillary fused silica column (length 10 m, internal diameter 0.32 mm) with CP-Sil-5-CB (Chrompack, Middelburg, The Netherlands) as the stationary phase. The operating temperatures of the injection port, column oven and detector were 300°C, 230°C, and 300°C, respectively. Helium was used as the carrier gas (flow rate 4 ml/min), and an auxiliary flow of helium (26 ml/min) was fed into the detector. The coefficient of variation of the gas chromatographic method did not exceed 5% in the alfentanil concentration range encountered in this study.

### DATA ANALYSIS

For each patient the presence or absence of responses during surgery and the corresponding plasma concentrations were entered in a nonlinear regression computer program (ELSFIT\textsuperscript{7}), which fitted the data according to the following version of the Hill equation\textsuperscript{12}:

$$\text{probability of no response} = \frac{C_p^\gamma}{C_p^{50 \gamma} + C_p^\gamma}$$

where $C_p$ is the measured plasma alfentanil concentration, $C_p^{50}$ is the concentration at which the probability of no response is 50%, and $\gamma$ is a dimensionless parameter reflecting the slope of the response curve. The alfentanil plasma concentration versus probability of no response curve for surgical stimulation during the procedure was determined for each patient.

Data are reported as mean ± SD or the incidence of observations unless specified otherwise. A two-sample $t$ test was used for intergroup comparisons. $P < 0.05$ was regarded as statistically significant.

### Results

The groups were comparable with respect to age, weight, duration of anesthesia, and the percentage of anesthesia time during which a response to the fourth stimulus of the train-of-four was present (table 1). Four patients in group 1 and two patients in group 2 were smokers (<10 cigarettes per day). Blood loss did not exceed 350 ml in any patient. The alfentanil dose requirement was significantly higher in group 1 (table 1). There was no difference in the degree of plasma protein binding between the groups (table 2).

In two patients in group 1 the initial target alfentanil plasma concentration (350 ng/ml) did not result in loss of consciousness within 2 min. Consciousness was lost when the target concentration was increased to 450 and 600 ng/ml, respectively. All patients in group 2 lost consciousness within 2 min of starting the alfentanil infusion. One patient in group 1 developed muscle rigidity. Bradycardia of 42 beats/min occurred in one patient in group 2. The heart rate was restored to pre-induction values following administration of atropine, 0.25 mg iv. None of these side effects recurred during anesthesia.

Figure 1 shows for each patient the alfentanil plasma concentrations associated with the presence or absence of a response to surgical stimulation. The type and number of responses observed during surgery are shown in table 3. All responses were rapidly controlled by increasing the target alfentanil plasma concentration. Systolic arterial pressure returned to normal within 1–8 min (median 2 min) in group 1 and within 1–6 min (median 2 min) in group 2.

### Table 1. Patient Details

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>45 ± 9</td>
<td>46 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66 ± 8</td>
<td>66 ± 5</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>151 ± 46</td>
<td>144 ± 26</td>
</tr>
<tr>
<td>% of anesthesia time with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>response to fourth stimulus of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>train-of-four</td>
<td>90 ± 7</td>
<td>92 ± 8</td>
</tr>
<tr>
<td>Mean alfentanil dose rate (µg·kg·min\textsuperscript{-1})</td>
<td>3.7 ± 1.2*</td>
<td>1.9 ± 0.4*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

* Difference between groups 1 and 2: $P < 0.005$. 

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\textsuperscript{7} Sheiner LB: ELSFIT—a program for the extended least squares fit of individual pharmacokinetic data. Technical Report, Division of Clinical Pharmacology, University of California, San Francisco, February, 1981.

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Table 2. Free Fraction (fₚ) of Alfentanil in Individual Patients

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
<td>fₚ</td>
</tr>
<tr>
<td>1</td>
<td>0.094</td>
</tr>
<tr>
<td>2</td>
<td>0.070</td>
</tr>
<tr>
<td>3</td>
<td>0.081</td>
</tr>
<tr>
<td>4</td>
<td>0.102</td>
</tr>
<tr>
<td>5</td>
<td>0.057</td>
</tr>
<tr>
<td>6</td>
<td>0.073</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.080 ± 0.016</td>
</tr>
</tbody>
</table>

group 2. Heart rate returned to normal within 1–6 min (median 2 min) in group 1 and within 1–2 min in group 2.

The fitted plasma concentration versus probability of no response curves for each patient are shown in figure 2. The calculated Cp₉₀ values and slopes (γ) of these curves are shown in table 4. The Cp₉₀ was significantly higher in group 1 than in group 2.

Naloxone was needed to restore adequate spontaneous ventilation in one patient in group 1 (0.04 mg) and in two patients in group 2 (0.04 and 0.08 mg). The plasma concentration at extubation in the patients who did not need naloxone was 372 ± 114 ng/ml in group 1 and 176 ± 39 ng/ml in group 2. This difference was highly significant (P < 0.005). The average Pₐ₅₀ values, determined 15, 30, and 60 min after extubation were 45 ± 8, 45 ± 7, and 43 ± 5 mmHg in group 1 and 43 ± 9, 43 ± 5, and 43 ± 7 mmHg in group 2, respectively.

Two patients in group 1 complained of nausea. In group 2 four patients complained of nausea and two of these vomited. When questioned on the day after surgery, no patient had any recall of the anesthesia or surgical period.

Discussion

We studied patients with the same disease state undergoing the same standard surgical procedure to minimize variability in the pharmacodynamics of alfentanil.

A possible criticism of this study is that it was not performed in a double-blind manner. However, to minimize investigator bias, changes in the target plasma concentration of alfentanil were based on strictly defined objective criteria, which had to be agreed upon by two observers, one of whom was blinded to the drinking history of the patient.

In patients with an average daily consumption of 20–40 g ethanol, the Cp₉₀ of alfentanil for the surgical procedure was more than double that of patients who were abstainers. A similar difference was found for the plasma concentration at which ventilation was adequate. In The Netherlands an average daily consumption of 20–40 g ethanol is considered as the upper limit of social drinking behaviour. The results of this study suggest that a cross-tolerance exists between alfentanil and ethanol.

Tolerance is a condition of a progressively decreasing response to the same dose of a drug, or conversely, the requirement that the dose must be progressively increased to maintain the same intensity of effect after each dose. Cross-tolerance usually involves drugs that are closely related pharmacologically, but not necessarily so. Tolerance can be either pharmacokinetic or pharmacodynamic in origin. Pharmacokinetic tolerance results from changes in the pharmacokinetic properties of a drug, such that reduced concentrations are present at the site of drug

![GROUP 1](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931358/)

![GROUP 2](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931358/)

Fig. 1. The plasma concentrations of alfentanil associated with responses and no responses during surgery in alcohol consumers (group 1) and alcohol abstainers (group 2). Each horizontal line represents one patient. A response is indicated by a downward deflection. No response is indicated by an upward deflection. V, W, X, Y, and Z represent the surgeons.
### TABLE 3. Type and Number of Responses during Surgery

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>Range per Patient</th>
<th>N</th>
<th>Range per Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>S + BP + R</td>
<td>4</td>
<td>0–3</td>
<td>2</td>
<td>0–1</td>
</tr>
<tr>
<td>BP + R</td>
<td>2</td>
<td>0–1</td>
<td>1</td>
<td>0–1</td>
</tr>
<tr>
<td>S + R</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0–1</td>
</tr>
<tr>
<td>S</td>
<td>5</td>
<td>0–3</td>
<td>6</td>
<td>0–2</td>
</tr>
<tr>
<td>BP</td>
<td>17</td>
<td>0–6</td>
<td>14</td>
<td>0–4</td>
</tr>
<tr>
<td>R</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0–1</td>
</tr>
<tr>
<td>OAS</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0–1</td>
</tr>
</tbody>
</table>

N = number of responses; S = somatic response; BP = systolic arterial pressure above normal + 15 mmHg; R = heart rate above 90 beats/min; OAS = other autonomic signs (flushing).

### TABLE 4. C\(p_{50}\) and \(\gamma\) for Surgical Operation in Individual Patients

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
<td>(C_{p_{50}} \pm SE) (ng/ml)</td>
</tr>
<tr>
<td>1</td>
<td>453 ± 58</td>
</tr>
<tr>
<td>2</td>
<td>721 ± 36</td>
</tr>
<tr>
<td>3</td>
<td>504 ± 32</td>
</tr>
<tr>
<td>4</td>
<td>559 ± 54</td>
</tr>
<tr>
<td>5</td>
<td>474 ± 62</td>
</tr>
<tr>
<td>6</td>
<td>442 ± 85</td>
</tr>
<tr>
<td>Mean</td>
<td>522*</td>
</tr>
<tr>
<td>SD</td>
<td>104</td>
</tr>
</tbody>
</table>

SE = standard error of the parameter estimated by nonlinear regression; SD = standard deviation of the mean.

* Difference between groups 1 and 2: \(P < 0.001\).

A common mechanism underlying pharmacokinetic tolerance is an increased rate of metabolism, e.g., tolerance to barbiturates as a result of enzyme induction. Pharmacodynamic tolerance results from adaptive changes at the site of action, such that both the concentration at the site of action and the plasma concentration of a drug must be increased to achieve a given effect. We found that higher total plasma alfentanil concentrations were required in alcohol consumers than in abstainers. Because the alfentanil protein binding was similar in both groups, the concentration of free (unbound) alfentanil was also higher in the patients who were regular consumers of alcohol. Because it is the concentration of free drug that is in equilibrium with the concentration at the site of action, it can be concluded that the tolerance to alfentanil in alcohol consumers is primarily pharmacodynamic rather than pharmacokinetic in origin.

Chronic alcohol consumption produces substances that act as opioid agonists. Ethanol alters the metabolism of biogenic amines, e.g., dopamine. Acetaldehyde, the primary metabolite of ethanol, condenses directly with dopamine and also induces condensation reactions between dopamine and dopaldehyde by inhibiting aldehyde dehydrogenase. The condensation products salsolinol and tetrahydropapaveroline have addictive properties, bind to opioid receptors, have antinociceptive effects with a potency comparable to the enkephalins, and their effect is blocked by naloxone. The opioid-like effects of these two substances may induce tolerance to opioids.

Ethanol modulates opioid receptors in cultured neural cells. The immediate effect of relatively low concentrations of ethanol (1.15–2.3 g/l) is an inhibition of opioid receptor binding. Exposure of neural cells to ethanol for 2 weeks induces a large, possibly adaptive, increase in the number of opioid binding sites. If this response also occurred in vivo, it could further explain the ability of ethanol to induce tolerance to alfentanil.

Opioids affect both the firing of dopamine neurons and the metabolism of dopamine at the terminals of the nigrostriatal dopaminergic pathway. Morphine promotes both dopamine synthesis and release in mouse striatum. However, mice rendered tolerant to and dependent on ethanol are less responsive to morphine's effects on striatal dopamine metabolism than control animals. A decrease in the affinity of striatal opioid receptors for \(^{3}H\)dihydromorphone also has been demonstrated. These ethanol-induced changes may also alter pharmacologic effects of opioids.

In conclusion, we have demonstrated that in patients who are regular consumers of alcohol higher concentrations of alfentanil are required to suppress responses to surgery than in a similar group of patients who are abstainers. This difference in the pharmacodynamics of alfentanil is attributed to an ethanol-induced pharmacodynamic tolerance. This study was performed in patients.
undergoing breast surgery. It is likely that our conclusions would also be valid for patients undergoing other types of surgery and that a similar pharmacodynamic tolerance occurs in males, and for other opioids.

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References
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