# Review Article

# The pharmacokinetic behaviour of opioids administered during cardiac surgery

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*Cardiac surgery with hypothermic cardiopulmonary bypass (CPB) is among the most commonly performed operations in Canada today. The potential effects of hypothermia and CPB on the disposition of certain opioids are reviewed. Reasons for prolongation of the elimination half-time of the opioids used during cardiac surgery are explored. The roles that age, hypothermia, protein binding and drug sequestration may play in changing opioid pharmacokinetic behaviour are examined and suggestions for future research are made.*

*La chirurgie cardiaque avec CEC hypothermique est parmi l'une des opérations les plus fréquentes de nos jours au Canada. Les effets potentiels de l'hypothermie et la CEC sur la disposition de certains opiacés sont revus. Les raisons de la prolongation du demi-temps d'élimination des opiacés utilisés lors de la chirurgie cardiaque sont explorées. Le rôle de l'âge, l'hypothermie, la lésion protéique et la séquestration des médicaments dans l'altération de la pharmacocinétique des opiacés sont examinés et des suggestions pour des recherches futures sont suggérées.*

**Key words**

ANAESTHESIA: cardiac;
ANAESTHETICS, INTRAVENOUS: alfentanil, fentanyl, sufentanil;
PHARMACOKINETICS;
SURGERY: cardiac, cardiopulmonary bypass.

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Surgical procedures for cardiac disease are among the most commonly performed operations in North America. Hypothermia and cardiopulmonary bypass (CPB) may produce changes in the pharmacokinetic (changes in drug distribution and clearance) and pharmacodynamic (changes in drug effect) behaviour of anaesthetic drugs employed during cardiac surgery.[1,2]

High doses of opioids play an important role in the modern anaesthetic management of cardiac surgical patients.[3-7] To avoid the intraoperative awakening which may occur when opioids are employed alone[8,9] and reflex autonomic stimulation due to inadequate plasma concentrations,[4-6,10] fentanyl and other opiates are supplemented with other CNS depressants, either in the premedication[11] or as part of the maintenance phase of the anaesthetic.[3,5,7,10,12] Such combinations may produce haemodynamic instability[13] and prolong times to recovery of spontaneous ventilation in the postoperative period.[3] Administration of nalbuphine to reverse the respiratory depression produced by fentanyl has been tried but produces serious adverse sequelae.[14]

A more rational approach would be to characterize the relevant changes in opioid pharmacokinetic and pharmacodynamic behaviour produced by disease, hypothermia

and cardiopulmonary bypass. Thereafter, it might be possible to design and test anaesthetic protocols involving different drug combinations (e.g., midazolam) in a quantitative fashion against a background of stable plasma opioid levels.[15] This would provide adequate anaesthesia yet still allow for early recovery and mobilization. Towards this goal, this paper will review the developments in our understanding of the alterations in opioid pharmacokinetic and pharmacodynamic behaviour occurring during cardiac surgery.

## Potential changes produced by cardiopulmonary bypass

A variety of factors has considerable potential for altering drug pharmacokinetic and pharmacodynamic behaviour during CPB. Haemodilution by the priming solution of the CPB apparatus alters plasma protein concentrations and produces potential shifts in drug-protein binding.[1] An increase in the volume of distribution due to the pump volume may occur and binding to constituent parts of the bypass apparatus, including the oxygenator, has been described.[16–19] Cardiopulmonary bypass may alter organ blood flow, especially to clearance organs such as the liver, kidneys, and lung.[20–22] Such complex interactions make the study of pharmacokinetic and pharmacodynamic changes produced by CPB a challenge. Activation of complement and formation of microemboli[23] by the apparatus could lead to microinfarcts in all organs including the brain and this could be one of the explanations for the altered CNS sensitivity to enflurane.[24]

## Chances in elimination half-time

Perhaps one of the easiest variables to measure and determine whether a change in pharmacokinetic behaviour has occurred is the elimination half-time ($t_{\frac{1}{2}}\beta$). This variable is influenced by changes in either the volume of distribution ($V_D$), clearance (Cl), or both:[25]

$$t_{\frac{1}{2}}\beta = \frac{0.693\ V_D}{Cl}$$

It is not necessary to know which of these factors, i.e., clearance or volume of distribution, has changed to demonstrate a change in elimination half-time since it can be estimated by examining the terminal phase of a concentration vs time curve for the drug in question.

### *Fentanyl*

Koska *et al.* studied patients having coronary artery bypass graft (CABG) surgery and compared their results with a group of patients having major vascular surgery.[20] Patients received fentanyl 0.50 mg · 70 kg$^{-1}$ and plasma fentanyl levels were measured over time. Liver blood flow was measured by an indocyanine green dye clearance methodology. Pharmacokinetic variables were calculated following determination of the best-fit concentration vs time curve using a least-squares non-linear regression technique (control group) or from the terminal log linear portion of the decay curve using linear regression of the natural logarithm of plasma fentanyl concentration vs time (CPB group). The authors commented that CPB changed the concentration vs time curve from the classical shape by introducing a plateau during the period of CPB. These authors showed that liver blood flow was reduced (to 70% of normal) during and following separation from CPB. They suggested that this was responsible for the prolonged elimination half-time (5.2 ± 2.7 vs 3.3 ± 1.1 hr) when compared with their control group. However, several flaws in the study design make the interpretation of these results difficult. As described, the methods for determining the relevant pharmacokinetic variables differed in the two groups. In the group receiving CPB, the method used may have led to overestimation of the elimination half-time and this makes between-group comparisons suspect. Furthermore, the concentrations in plasma were only measured for 6–7 hr. It is generally recommended that sampling continue for at least three half-times to characterize fully the elimination portion of the concentration vs time curve. With a reported elimination half-time of 5.2 hr, sampling for 20–24 hr would be necessary. Finally, a plateau was also seen in the concentration vs time curve shown for one of their control patients (Figure 2 in the original article). Such plateaus suggest that elimination was not uniform in their control group either.

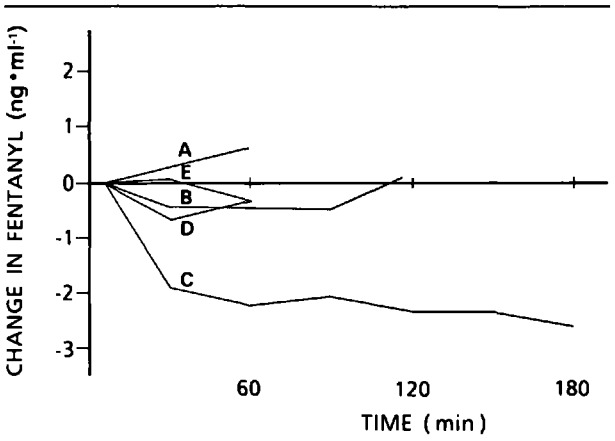


FIGURE 1 Changes in plasma fentanyl concentrations (ng · ml$^{-1}$) in five patients (A–E) during cardiopulmonary bypass. Changes are measured from the concentration at the start of bypass. (Reprinted with permission.)[26]

Bovil and Sebel examined the changes in fentanyl pharmacokinetics in five patients having cardiac surgery.[26] Chronic cardiac medications were continued and

lorazepam 5 mg *po* was given 1.5 hr before surgery as pre-medication. Fentanyl 60 $\mu g \cdot kg^{-1}$ was administered *iv* over two minutes. A bubble oxygenator was employed with hypothermia to 25° C, CPB flow rate of 50 $ml \cdot kg^{-1} \cdot min^{-1}$ and haemodilution to a haematocrit of 20–25%. Plasma fentanyl concentrations were determined over time until 24 hr after induction of anaesthesia. With the onset of CPB, there was a decrease of 53% in the plasma fentanyl concentration. Thereafter, there was a relative plateau in the fentanyl concentrations during CPB (Figure 1). Following separation from CPB, there was an initial plateau in the concentration vs time curve and then an exponential decay with a $t_{\frac{1}{2}}\beta$ of 7.1 ± 0.6 hr. This is longer than that previously published for healthy young adults (3.7 ± 0.38 hr).[27] The authors attributed this difference to age, hypothermia, and the effects of CPB including haemodilution.

*Alfentanil*

Robbins *et al.* studied 28 patients with preserved ventricular function.[28] Premedication consisted of morphine, scopolamine, and diazepam. Patients in Group I ($n$ = 8) received alfentanil 250 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ for one hour with a simultaneous maintenance infusion of 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Patients in Group II ($n$ = 10) received 300 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ for one hour with a maintenance infusion of 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and those in Group III ($n$ = 10) received 350 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ with a maintenance infusion of 3.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The authors sought to determine the concentration vs effect relationship for alfentanil in cardiac surgical patients and the pharmacokinetic and pharmacodynamic profile for alfentanil following CPB. Total alfentanil concentrations in plasma were measured. There were no differences observed among groups (Group I, 7/8; Group II, 6/10; Group III, 7/10) in the number of patients responding to noxious stimulus. No significant differences were observed in the plasma concentrations among the three groups although Group III (highest infusion rate) tended to have the highest concentrations. Plasma concentrations increased during the initial one hour after bolus and infusion. After one hour, coincident with the onset of CPB, plasma concentrations decreased and then a plateau was observed. Following CPB, plasma concentrations declined steadily. No concentration vs effect relationship could be identified (confirming data previously reported by Hug *et al.*).[11] The elimination half-time was prolonged to 5.1 ± 1.0 hr compared with 1.5 hr in healthy adults. Awakening time was 3.2 ± 0.6 hr and tracheal extubation occurred at 8.8 ± 1.2 hr. Why the three infusion schemes failed to provide different plasma concentrations is not discussed but could be related to the infusion methodology (the infusion scheme employed failed to account for distributive losses), or that the differences in the doses administered were not sufficiently great to produce a difference in the resultant plasma concentrations given the 20–30% variability in alfentanil plasma concentrations known to be present in the population as a whole.[29] Targeted plasma concentrations were not identified in the study. The one hour bolus/infusion may have obscured among group differences since CPB commenced when the infusion terminated. Finally, plasma concentrations were measured for only 11 hr which, given the prolongation in elimination half-time, was too short. Despite these methodological difficulties, it was concluded that the elimination half-time for alfentanil was prolonged following CPB. As discussed by the authors, the prolonged elimination half-time, and subsequent time to awakening and tracheal extubation, suggested that the pharmacokinetic advantages of alfentanil in healthy adults not undergoing cardiac surgery (e.g., short duration of action and rapid ability to obtund noxious stimuli) may be modified in cardiac surgical patients.

*Sufentanil*

Alvis *et al.* employed a computer-driven continuous infusion of fentanyl utilising pharmacokinetic values obtained from normal volunteers[27] and designed to produce a target plasma fentanyl concentration in a group of cardiac surgical patients.[30] Target plasma fentanyl levels were achieved. The computer-driven infusion system performed as well as manually administered fentanyl in controlling episodes of hypertension and tachycardia before CPB.

Flezzani *et al.* used the same system to administer a computer-driven infusion of sufentanil designed to provide stable plasma levels during cardiopulmonary bypass.[31] In ten patients undergoing elective coronary artery revascularization, sufentanil was administered by a computer-assisted infusion designed to produce plasma sufentanil concentrations of 5 $ng \cdot ml^{-1}$.[31] The infusion was initiated ten minutes before CPB and was based upon pharmacokinetic values obtained for sufentanil from a group of general surgical patients. Prior to CPB, the plasma sufentanil concentration was 3.8 ± 0.4 $ng \cdot ml^{-1}$. Concentrations declined to 2.5 ± 0.3 $ng \cdot ml^{-1}$ two minutes following initiation of CPB, with a gradual increase thereafter to 4.7 ± 0.4 $ng \cdot ml^{-1}$ over 90 min. The authors concluded that utilization of normal pharmacokinetic variables to provide a computer-assisted infusion produced stable targeted plasma sufentanil levels during CPB despite the many changes occurring at this time which might alter sufentanil pharmacokinetics. Stability of plasma sufentanil concentrations during CPB was also observed by Okutani *et al.*[32] but changes in elimination half-time were not studied.

Thus it appears that in otherwise healthy adults having

coronary artery revascularisation procedures opioids can be administered intravenously (by a computer-assisted infusion[30,31] or by a manual method[32]) to achieve a predictable plasma level which is reduced but stable during CPB. Prolongation of the elimination half-time has been demonstrated for fentanyl and perhaps for alfentanil and the potential exists for drug accumulation if the drug is administered frequently or by infusion in the post-CPB period.

*Paediatrics*

Koren *et al.* determined the pharmacokinetic variables of fentanyl in a paediatric population undergoing surgery for congenital heart disease.[33] Two groups of patients were studied. The first group of ten received fentanyl 50 $\mu g \cdot kg^{-1}$ over one minute, followed by a continuous infusion of either 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($n = 4$) or 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($n = 6$). The infusion was discontinued at the onset of CPB. Plasma fentanyl concentrations were relatively stable prior to CPB (range 35–42 $ng \cdot ml^{-1}$ for the high infusion group vs 25–33 $ng \cdot ml^{-1}$ for the low infusion group). Onset of CPB resulted in a 71% reduction in plasma fentanyl levels, which was greater than that predicted by haemodilution alone. Plasma fentanyl concentrations were stable thereafter during hypothermic CPB. A second group of nine patients received fentanyl 30 $\mu g \cdot kg^{-1}$ over one minute with a maintenance infusion of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ based on pharmacokinetic variables determined in the first group. In the second group of nine patients, stable plasma concentrations of 23 $ng \cdot ml^{-1}$ were achieved. The authors suggested that children with intracardiac anomalies have up to a 300% higher plasma fentanyl level when dosed according to protocols developed in adults for fentanyl administration before CPB. Values for distribution half-time ($t_{\frac{1}{2}}\alpha$ = 12 ± 9 min), elimination half-time ($t_{\frac{1}{2}}\beta$ = 141 ± 98 min), and clearance (Cl = 12.8 ± 73 $ml \cdot kg^{-1} \cdot min^{-1}$) were not different from adults. However, the volume of distribution ($V_D = 1.4 \pm 0.9\ L \cdot kg^{-1}$) was significantly less than that reported for adults (4-5.9 $L \cdot kg^{-1}$). The authors concluded that the increased plasma fentanyl concentrations relative to adults in the pre-bypass period were secondary to the reduced volume of distribution. This smaller distribution volume in children with intracardiac shunts could be related to the existence of congestive heart failure, alterations in extravascular fluid compartments, changes in blood volume, altered protein binding, or changes in lung sequestration of fentanyl due to changes in pulmonary blood flow. The authors suggested that dosing for children with complex congenital heart disease should be based on kinetics obtained in this population, rather than adults, and suggested that if adult dosing schemes are used, they will lead to plasma levels much in excess of that required for haemodynamic stability. Unfortunately, the authors did not carry their observations into the post-CPB period. Consequently, the effect that CPB and repair of the congenital lesion would have on fentanyl pharmacokinetic variables in the post-CPB period is entirely speculative.

There are several concerns which may have influenced the interpretation of the pharmacokinetic data reported. The authors did not state the time period over which fentanyl samples were collected. This is crucial information since it is from these data that pharmacokinetic variables are calculated. For example, if sampling was restricted to the period prior to CPB alone, insufficient time would have elapsed to allow for an accurate description of the elimination phase. On the other hand, if sampling continued into the postoperative period, how was the 71% reduction in plasma fentanyl levels during CPB handled? The duration of postoperative sampling would affect the description of the elimination phase of the concentration vs time curve and the determination of such pharmacokinetic variables. If large changes from normal are detected (as for the volume of distribution in this study) it is important that they be identified as true changes, not merely changes produced as artifacts due to study methodology. While not stated, presumably the authors recognized that some of these difficulties could affect the interpretation of their results because the second part of their study was performed utilising the pharmacokinetic variables determined in their initial patients and they were able to achieve and maintain the desired target plasma fentanyl level. This suggests that the results obtained from their initial patients reflected true pharmacokinetic changes.

One other methodological issue which arises from this study is the question of whether the data best fitted a one-, two-, or three-compartment model as described in classical pharmacokinetic terms.[25] This is done by fitting the data to a statistical model[34] and should be done for any set of concentration vs time data as it allows for the most accurate description of pharmacokinetic values. Such was not the case in this study.

Koren *et al.* examined the question of age- and disease-related factors in an extension of the previous study.[35] Nineteen infants and children were studied as described above and all the caveats with respect to data interpretation still apply. When examined for age-related differences, clearance of fentanyl was increased with decreasing age. On the other hand, older children with tetralogy of Fallot (and presumably less severe disease as indicated by higher arterial oxygen partial pressures) had an increased volume of distribution which was more like that observed in adults. In children with congenital heart disease it would seem that alterations in the distribution

volume of fentanyl may depend on the severity of the haemodynamic disturbance whereas changes in clearance depend on age. Whether such alterations persist into the post-bypass period following correction of the cardiac anomaly is unknown. Further studies which correct the methodological issues described are warranted.

Davis *et al.* examined the pharmacokinetic behaviour of sufentanil in a paediatric cardiac surgical population, some of whom underwent surface cooling.[36] Following sufentanil 15 $\mu g \cdot kg^{-1}$, three groups of patients were studied before initiation of CPB. Group 1 consisted of seven children younger than ten months who were not surface-cooled. Group 2 ($n = 6$) consisted of seven children older than ten months while Group 3 ($n = 7$) consisted of children less than ten months of age who were surface-cooled. The elimination half-time was prolonged in the group of children receiving surface-cooling (120 vs 53 min). Children less than ten months old and who were not surface-cooled had a smaller volume of distribution (1.6 vs 3–3.7 $L \cdot kg^{-1}$). The clearances did not differ statistically among the groups but the younger children who were not surface-cooled had a higher clearance than the older children (28 vs 18 $ml \cdot kg^{-1} \cdot min^{-1}$). Taken as a whole, these findings are similar to those determined by Koren *et al.* for fentanyl.[33] Thus, for high potency opioids, it appears that compared with older children and adults, younger children with cardiac disease have smaller volumes of distribution (disease-related) and increased clearances (age-related). However, some of the same methodological criticisms levied at the studies of Koren *et al.* also apply here. This study defined the sampling times and duration (restricted to the pre-CPB period). This avoided the difficulties in interpretation of changes in plasma levels associated with haemodilution and reductions in plasma sufentanil levels during CPB. However, sampling was carried out for a maximum of two hours. This is insufficient to describe accurately the elimination phase of the concentration vs time curve (three elimination half-times = 9–15 hr). Clearly this is impossible within the context of a clinical study involving patients about to undergo cardiac surgery. Instead, the result will be a truncated data set which will usually result in an apparently reduced elimination half-time and an increased plasma clearance. This is a common problem in studies of this nature and one to which the reader should be alerted when reviewing studies of similar protocols. Infusion schemes based on these clearance values may result in plasma levels higher than anticipated. While this is unlikely to be of much clinical importance for opioids (other than perhaps an increased incidence of side-effects including respiratory depression), for drugs with a much narrower therapeutic index, the results might be potentially hazardous. To eliminate the confounding methodological issues, a further study designed to produce stable plasma levels based on the pharmacokinetic variables determined in the original study is required.

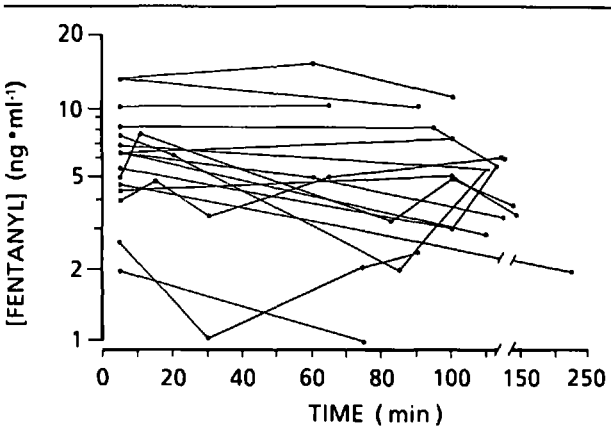


FIGURE 2 Fentanyl plasma concentrations in 18 children during profound hypothermia (18–25° C). Time zero is the initiation of cardiopulmonary bypass. (Reprinted with permission.)[16]

*Hypothermia*

The role of hypothermia in altering the pharmacokinetic behaviour of drugs employed during cardiac surgery has not been well studied. While CPB can be conducted at normothermia, it is usually conducted under hypothermic conditions (temperatures of 25–30° C in most adult patients). Hypothermia itself, independent of changes produced by CPB, may influence drug metabolism, distribution, and effect. *In vitro*, hypothermia has been shown to reduce the metabolism of propranolol and verapamil due to a reduced affinity of the microsomal enzymes for the drugs.[37] In addition, there may be a reduced binding affinity of opiate receptors for certain opioids under hypothermic conditions.[38] The metabolism of a weak acid (sulfanilamide) was demonstrated to be relatively unchanged whereas that of a weak base (atropine) showed marked temperature dependence.[39,40] Opiates such as fentanyl, which are weak bases and metabolised by microsomal enzymes, might be expected to have altered metabolism under conditions of hypothermic CPB. Binding to opiate receptors might be altered with a change in the pharmacodynamics of the drugs.

Koren *et al.* described a reduction in clearance (2.4 vs 0.7 $ml \cdot kg^{-1} \cdot min^{-1}$) in piglets subjected to hypothermia (29° C) while elimination half-time did not change (62 vs 85 min).[41] As part of the same study, fentanyl plasma concentrations in 18 children undergoing cardiac surgery with profound hypothermia (18–25° C) and CPB were measured. At the initiation of hypothermia, mean fentanyl plasma concentration was 6.5 $\mu g \cdot ml^{-1}$. After 100–140 min of hypothermia, plasma levels were essentially unchanged at 5.3 $ng \cdot ml^{-1}$ (Figure 2). This suggests that,

*in vivo*, fentanyl metabolism is impaired by hypothermia. This could lead to prolonged drug effects following CPB as patients are frequently hypothermic for varying periods of time following surgery.

### Changes in protein binding

Most drugs exist in plasma in two forms – free, i.e., unbound drug and bound (bound to plasma proteins).[42] It is the free drug which is the active moiety and which, in the case of opioids, binds to specific receptors. Basic drugs such as fentanyl, sufentanil and alfentanil are bound to both plasma albumin and to other proteins such as $\alpha_1$-acidglycoprotein.[43] Binding to $\alpha_1$-acidglycoprotein can be substantial.[43] Under conditions of stress, plasma $\alpha_1$-acidglycoprotein concentration may increase as it is an acute phase reactant.[44] The importance of measuring changes in free vs total concentrations of drug in plasma was highlighted in a study by Kumar *et al.*[45] They postulated that haemodilution might have an effect on the unbound fraction of drug. Five patients undergoing CABG were studied. Alfentanil was administered as a rapid loading infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ followed by a maintenance infusion of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for a duration of 3.35 ± 0.28 hr. Using a Cobe Optiflow II® membrane oxygenator, CPB was conducted with an in-line arterial filter, a crystalloid priming solution for the CPB apparatus containing one litre of fractionated pooled human plasma, and hypothermia to 28° C. Free and total plasma alfentanil concentrations were determined using an ultrafiltration technique. Plasma alfentanil levels were stable before initiation of CPB. At the onset of CPB, total plasma alfentanil levels decreased (177 ± 44 to 92 ± 29 $\mu g \cdot L^{-1}$) but the unbound concentration showed little change (29 ± 12 vs 35 ± 20 $\mu g \cdot L^{-1}$). This led to an overall increase in the unbound fraction from 0.16 ± 0.04 to 0.35 ± 0.08 (Figure 3). Toward the end of CPB (two hours) the mean total alfentanil concentration had increased to 155 ± 82 $\mu g \cdot L^{-1}$ while the unbound concentration remained essentially unaltered (31 ± 13 $\mu g \cdot L^{-1}$). Plasma albumin and $\alpha_1$-acidglycoprotein concentrations decreased to 50% of their pre- CPB level with a strong correlation between the binding ratio (bound/ unbound drug) of alfentanil and plasma $\alpha_1$-acidglycoprotein concentrations. This study has important clinical implications since it is the unbound drug which is the active moiety and it appears that the unbound concentration changes very little during CPB. Similar results have been demonstrated for methohexital and thiopentone.[46]

### Drug sequestration

*Lungs*

The possibility of drug sequestration in the lungs was examined by Bentley *et al.*[22] They initially examined

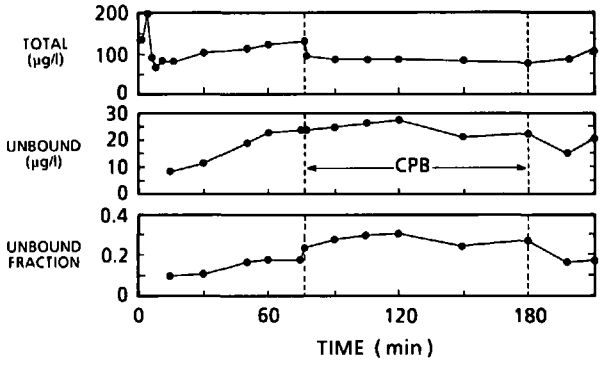


FIGURE 3 Total and unbound plasma concentrations and unbound fraction of alfentanil in a patient during continuous infusion of alfentanil. The horizontal arrows indicate the times of onset and cessation of bypass. (Reprinted with permission.)[45]

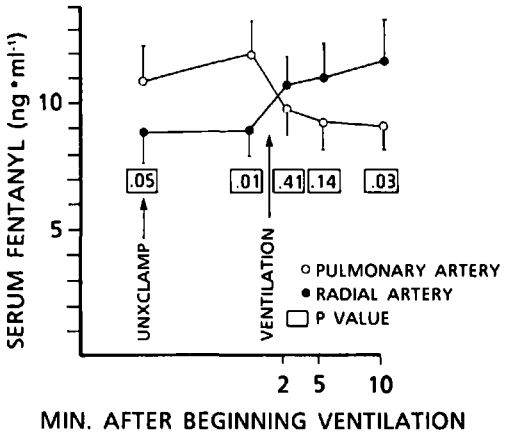


FIGURE 4 Mean fentanyl concentrations in seven patients before and after ventilation and perfusion to lung are restored near the end of cardiopulmonary bypass. (UnXclamp = removal of aortic cross clamp). (Reprinted with permission.)[22]

changes in plasma fentanyl concentrations in five patients receiving 100 $\mu g \cdot kg^{-1}$ over five–ten minutes. Following the onset of CPB, plasma fentanyl concentrations decreased from 17 ± 1 $ng \cdot ml^{-1}$ to 9 ± 1 $ng \cdot ml^{-1}$ and remained stable thereafter. However, with the resumption of mechanical ventilation prior to separation from CPB, plasma levels increased. A further seven patients were studied and, in this group, plasma concentrations in pulmonary artery and radial artery samples drawn simultaneously were measured. With the onset and maintenance of cardiopulmonary bypass, pulmonary artery concentrations exceeded radial artery levels until resumption of mechanical ventilation. At this time there was a reversal in the concentration differences with an increase in systemic arterial concentrations and a decrease in pulmonary artery levels (Figure 4). It was concluded that

during CPB the lungs act as a storage depot for fentanyl. With reperfusion shortly before termination of CPB, fentanyl was washed out from the lungs and this may be one explanation for the persistence of plasma fentanyl concentrations following termination of CPB. A similar rise in plasma sufentanil levels at the end of CPB was also demonstrated by Okutani *et al.*[32] These studies suggest that during CPB, basic drugs such as fentanyl may be sequestered in the lungs and that washout of the agent occurs with resumption of normal circulation and ventilation. The present author speculates that the increase in plasma levels of opioids at this time may be one explanation for the reduced requirements for anaesthetic supplementation following termination of CPB.

*Cardiopulmonary bypass apparatus*

The binding of opioids to components of the cardiopulmonary bypass apparatus and ancillary equipment has been addressed in several recent studies.[16-19,47,48] Koren *et al.* observed a consistant decline in plasma fentanyl concentrations in paediatric patients with the onset of CPB.[16] This decline was greater than was predicted on the basis of haemodilution alone. They administered fentanyl as a bolus followed by a maintenance infusion to 19 children. The infusion was discontinued at the onset of CPB. In the first ten patients no fentanyl was added to the priming solution in the CPB apparatus. In patients #11–19, fentanyl 20 ng · ml$^{-1}$ was added to the priming solution. Plasma levels of fentanyl were stable before CPB and declined by 74 ± 9% with the onset of CPB. Priming of the CPB circuit with fentanyl 20 ng · ml$^{-1}$ did not prevent the decline in plasma fentanyl concentrations (76 ± 7% vs 72 ± 10%). This group of investigators then carried out a series of *in vitro* experiments including addition of fentanyl 120 ng · ml$^{-1}$ to a closed circuit comprising pvc tubing, the oxygenator, and primed with 500 ml of whole blood. Plasma fentanyl concentrations were measured at regular intervals following circulation. A steep decline in plasma fentanyl concentrations from 120 ng · ml$^{-1}$ to 2 ng · ml$^{-1}$ occurred within five minutes which then remained stable. Examination of this phenomenon by flushing fentanyl solution through various components of the circuit demonstrated sequestration of fentanyl by the oxygenator. The authors suggested that, at least in children, sequestration of fentanyl by the CPB apparatus might be sufficient to decrease plasma concentrations below the level necessary for a satisfactory analgesic/anaesthetic effect and that supplementation of fentanyl following the onset of CPB might be advisable.

Skacel *et al.* examined the *in vitro* binding of fentanyl and alfentanil to a circuit comprised of a Shiley S-100A bubble oxygenator, Pall Ultipor® blood filter, silicone pump head tubing, and Mediflex® perfusion tubing.[17] Alfentanil (500 ng · ml$^{-1}$) or fentanyl (100 ng · ml$^{-1}$) was

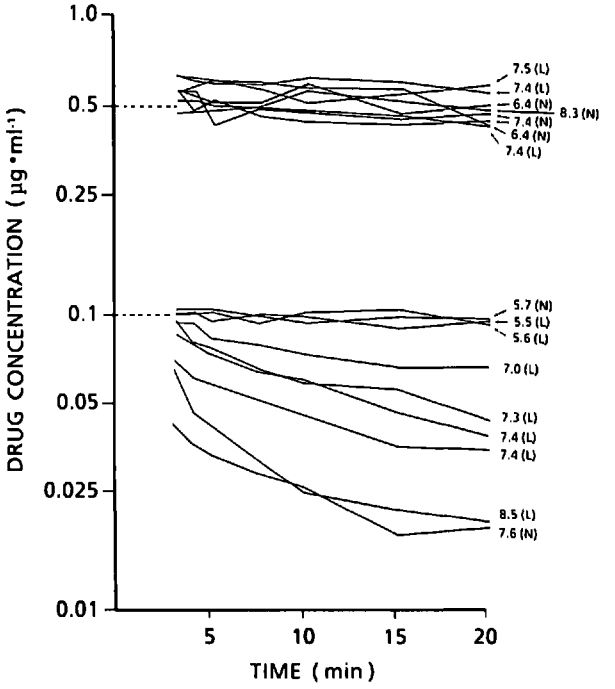


FIGURE 5 Changes in concentrations of alfentanil (top) and fentanyl (bottom) (shown on the same logarithmic scale – vertical axis) in extracorporeal circuit prime with time. Dotted lines represent predicted concentrations. Numbers on the right hand side are pH values of each priming solution. (L) = Low Temperature (24.4–25.7° C); (N) = Normothermic (34.1–37° C). (Reprinted with permission.)[17]

added to the priming solution and circulated for 20 min at a temperature dictated by the perfusionist and at various measured pH's. At pH > 7.0, fentanyl concentration declined progressively so that by 20 min the concentration was only 0.02–0.05 ng · ml$^{-1}$ (Figure 5). Alfentanil concentrations remained unchanged. Neither drug was affected by changes in temperature (to as low as 24.4° C). The authors suggested that since fentanyl is a lipophilic base with a pKa of 8.4, the degree of ionisation would be highly susceptible to changes in pH with a 24-fold increase in the non-ionised component over the pH range of 5.5–7. Increased free drug would allow for more binding to the extracorporeal circuit. Alfentanil (pKa 6.5), being less highly ionised, was less lipid soluble and therefore less susceptible to these changes. The relevance of these observations to the clinical situation is uncertain but they may be important depending on how blood gas assessments are managed during CPB.

Hynynen performed a series of *in vitro* and *in vivo* experiments to compare binding of fentanyl and alfentanil to the CPB apparatus and its clinical significance.[18] In the first set of *in vitro* experiments, a bypass circuit containing either a Shiley S-100A® bubble oxygenator or a Bentley BOS-CM50® membrane oxygenator was used. Fentanyl (30 ng · ml$^{-1}$) or alfentanil (1500 ng · ml$^{-1}$) was

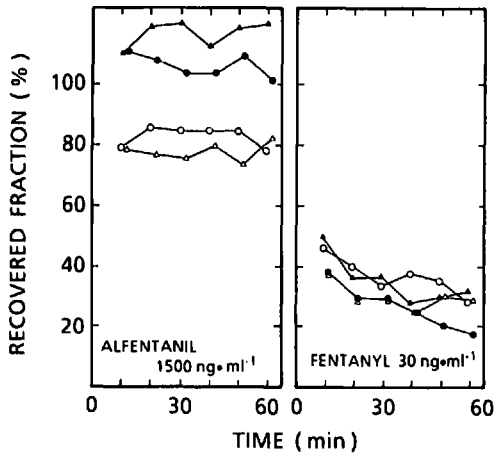


FIGURE 6 The fractions of the calculated alfentanil (1500 ng · ml$^{-1}$) and fentanyl (30 ng · ml$^{-1}$) concentrations recovered in the prime solutions during a 60 min circulation in a closed cardiopulmonary bypass system. Each line represents a single experiment. The constitution of the prime in the experiments with a bubble oxygenator is indicated as follows: ○ = without blood; ● = with blood, and that with a membrane oxygenator as follows: △ = without blood; ▲ = with blood. (Reprinted with permission.)[18]

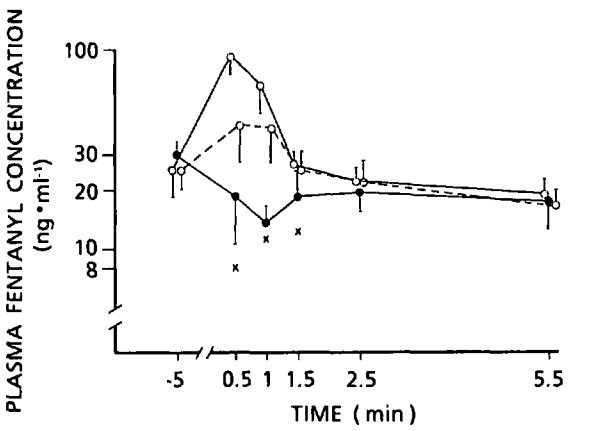


FIGURE 7 Plasma fentanyl concentrations (mean values ± SD) in patients connected to the cardiopulmonary bypass circuit with primes containing no fentanyl (●–●) or containing a calculated fentanyl concentration of 140 (○--○) or 280 (○–○) ng · ml$^{-1}$. X indicates the lowest drug concentration measured at each stage of the study during the first 1½ minutes of cardiopulmonary bypass in patients not receiving fentanyl in their prime. (Reprinted with permission.)[18]

added to the circuit. The pH and $PCO_2$ were maintained at normal levels. Closed circulation occurred for 60 min during which plasma opioid concentrations were measured. Marked decreases (73%) in fentanyl levels occurred over 60 min (Figure 6). No difference in the magnitude of decline in fentanyl concentrations was observed between the use of a bubble or membrane oxygenator or whether the priming solution contained blood or crystalloid solutions. In contrast, alfentanil plasma levels were relatively stable throughout (80% of predicted using a crystalloid priming solution). Addition of blood to the priming solution resulted in an increase in plasma alfentanil concentrations above the predicted value and this was attributed to a lower uptake of alfentanil by red blood cells or a higher degree of binding to plasma proteins compared with fentanyl.

In the *in vivo* studies patients received fentanyl or alfentanil 48 μg · kg$^{-1}$ as part of their anaesthetic. Fentanyl (140 or 280 ng · ml$^{-1}$), alfentanil (700 ng · ml$^{-1}$) or nothing was added to the CPB circuit ten minutes before the onset of CPB and circulation of the priming solution within the circuit allowed to occur. In the group of patients receiving fentanyl, concentrations in the bypass circuit declined to 67% (140 ng · ml$^{-1}$) or 57% (280 ng · ml$^{-1}$) over the ten-minute period. Addition of blood to the priming solution did not alter the degree of decline. Alfentanil concentrations did not decline over time from the initial level. Following the onset of CPB, plasma levels decreased in those patients receiving no opioid in the CPB priming circuit. This decline was prevented by addition of opioid to the priming solution (Figure 7). By 2.5 min after the start of CPB, plasma concentrations were similar irrespective of whether the circuit was primed with opioid or not. The author concluded that the initial decrease in plasma opioid levels with the initiation of CPB might expose patients to subanaesthetic concentrations and could be avoided by addition of drug to the priming solution or by supplementing the plasma concentration prior to initiation of CPB.

The exact binding site within the Scimed® membrane oxygenator was determined to be the silicone-based membrane sheets.[19] These investigators also demonstrated in this *in vitro* model that the process was saturable but unlikely to occur using concentrations employed clinically.

Two studies have examined whether blood conservation devices can remove opioids. Stone *et al.* examined the removal of sufentanil by haemoconcentrators or cell-savers.[47] They measured sufentanil levels in the supernatant from these devices and found negligible amounts of drug present. This led them to conclude that because sufentanil is a highly lipid soluble compound with large tissue reserves, little remains in the plasma compartment for removal by these devices.

Hanowell *et al.* examined the removal of fentanyl from the Autotrans BT.795® autotransfusion device.[48] Serum, heparinised saline, and normal saline separated from the cells were collected for measurement of fentanyl concen-

trations. Measured in this fashion, 74 ± 21% of the fentanyl was removed during processing of harvested blood for reinfusion. *In vitro*, fentanyl was added to a saline solution to measure uptake by the device itself. In addition to that removed by processing, 78% of the fentanyl added was removed in the saline trials suggesting binding of fentanyl to the apparatus itself. The clinical importance of this is small. As the authors pointed out, removal of 74% of the fentanyl from 1 L of blood scavenged from the field, assuming a blood volume of 5 L, would remove only 15% of fentanyl from the intravascular space. This is only a fraction of the total tissue level for the drug and thus unlikely to have a marked pharmacodynamic effect.

## Conclusions

Before the onset of CPB, infusions based on pharmacokinetic variables determined in other populations appear to achieve the desired target concentrations in otherwise healthy adult cardiac surgical patients, although further study is required. This may not be the case in children where clearance may increase with decreasing age while the volume of distribution is likely influenced by the magnitude of haemodynamic disruption (and in particular presence of heart failure) produced by the disease process.

Following the onset of CPB, there is an initial rapid decline in plasma concentrations with a subsequent elevation and plateau, albeit at levels below those present before the onset of CPB. Patients may thus be at risk for awareness during the initiation of CPB and steps should be taken to prevent this from occurring. Certain opioids are sequestered by the CPB apparatus itself. This sequestration is unlikely to have a major impact on plasma concentrations *in vivo* due to the large tissue reservoir which exists for these agents. During CPB, despite the haemodilution and decrease in total plasma concentrations, changes in alfentanil free drug concentrations appear to be minimal.

High potency opioids may be sequestered in the lungs during CPB. With resumption of blood flow to the lungs there is a washout of sequestered drug with an elevation of plasma opioid levels. The time course over which this process continues and its clinical importance are unknown.

In general, the elimination half-time is increased for opioids following CPB.

Future research should direct itself to the measurement of free and total drug levels during CPB, a further description of changes in protein binding, the design and implementation of studies to investigate alterations in pharmacodynamic behaviour, further characterisation of the role of hypothermia, and an expansion of the number and classes of drugs so characterised.

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