Paediatric and Perinatal Drug Therapy **Volume 4, Issue 3 2001**

Drug Disposition During Extracorporeal Membrane Oxygenation (ECMO)

Hussain Mulla Senior Clinical Pharmacist in Critical Care Medicine and Research Associate

University Hospitals of Leicester–De Montfort University, Centre for Pharmacy Practice Research, Glenfield Hospital, Leicester. Tel. +44 (0) 116 2502578; Fax +44 (0) 116 2563710; email hussain.mulla@uhl-tr.nhs.uk

Graham Lawson Principal Lecturer in Analytical Chemistry

Department of Chemistry, De Montfort University, Leicester

R. K. Firmin Consultant Cardiothoracic Surgeon and Director of ECMO

Glenfield Hospital, Leicester

David R. Upton Director, Centre for Pharmacy Practice Research

University Hospitals of Leicester–De Montfort University, Centre for Pharmacy Practice Research, Glenfield Hospital, Leicester

Abstract

Although the technology and application of ECMO has progressed rapidly in recent years, information on the disposition of drugs administered during ECMO is lacking. The results of many studies of drugs in cardiopulmonary bypass are cited but extrapolating these results to ECMO may not be straightforward because of the differences in the duration of the two support systems.

Certain characteristics of drugs may dictate whether pharmacokinetic and pharmacodynamic changes will occur during ECMO. Examples are volume of distribution, protein binding, their physico-chemical characteristics (potential for interaction with circuits), as well as physiological changes and the influence of injection sites and flow rates. These effects are reviewed, and it appears that, on initiation of ECMO, the rapid haemodilution that follows may result in acute changes in plasma concentrations with potentially unpredictable pharmacological effects. Evidence is also emerging that significant sequestration of opioids and benzodiazepines by components of the circuit may result in higher dose requirements. This is confirmed by retrospective prescription audits. As yet, definitive dosing recommendations are only available for gentamicin and vancomycin.

Further studies are required, not only to delineate the complex changes in drug disposition occurring during ECMO, but also to establish clear dosing guidelines.

Key words: Extracorporeal membrane oxygenation (ECMO) – Drug disposition – Drug sequestration – Neonate – Cardiopulmonary bypass (CPB) – Haemodilution

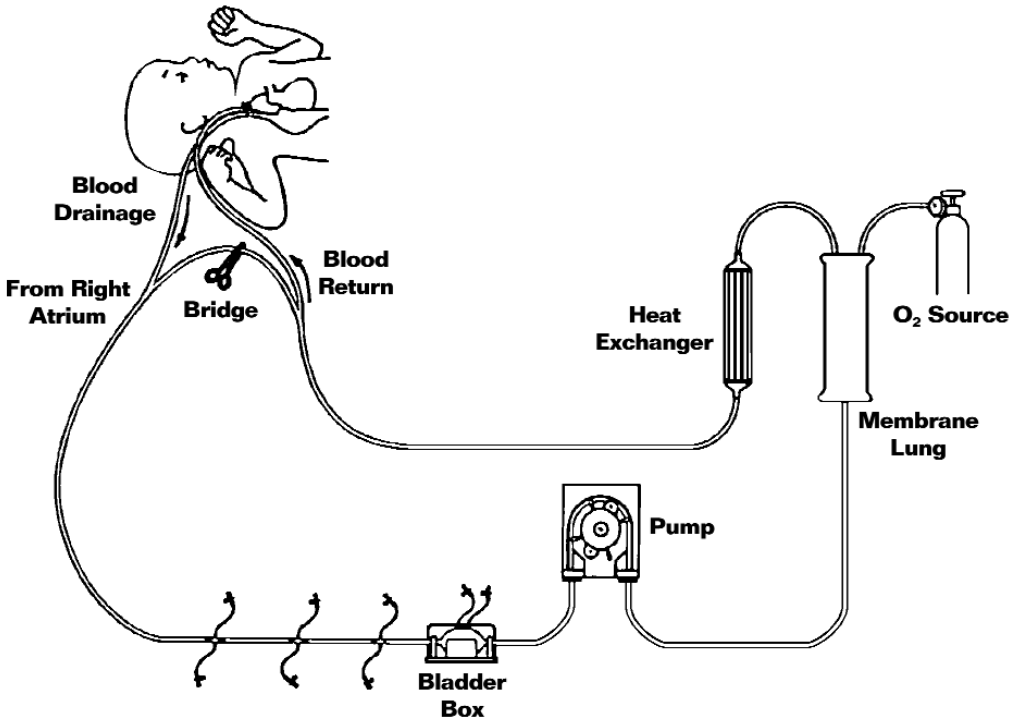

Figure 1. Schematic representation of the ECMO circuit

Introduction

ECMO is a complex life-support technique for critically ill patients which has been developed through modification of the heart–lung bypass machine. It is capable of sustaining life for days or weeks, permitting treatment and recovery during severe respiratory or cardiorespiratory disease. Over the last three decades, the technology has been developed and improved in the laboratory, investigated in clinical research settings and applied in routine clinical practice. Although the equipment and its application have changed and evolved over time, the basic concept of continuous extracorporeal circulation of blood to provide gas exchange and perfusion remains unaltered[1].

ECMO is now well established in the management of severe neonatal respiratory failure and has been shown to be superior to conventional therapy[2]. The support system is also applied in some centres for paediatric and adult respiratory failure and cardiac failure[3]. ECMO provides passive support of gas exchange and perfusion, thereby allowing implementation and optimisation of other forms of therapy to aid organ recovery. These include low-pressure, low-oxygen ventilator settings to avoid lung injury, bronchoscopy and lavage, diuresis and haemofiltration to dry weight, transfusion to normal haematocrit, full enteral or parenteral nutrition and drug therapy as indicated[1].

Pharmacological therapy in the ECMO patient presents a challenge since the continuous extracorporeal circulation of blood may conceivably impact on pharmacokinetics and pharmacodynamics. Despite the rapid advancement in many of the technical aspects of ECMO, much remains to be discovered regarding pharmacotherapy. The aim of this article is to review the current data available on drug disposition during ECMO and attempt to characterise the factors that may affect how drugs are 'handled'. Many of the previous studies investigating the impact of extracorporeal circuits on drug disposition have been in the context of cardiopulmonary bypass (CPB). These studies provide a useful introduction to the complexities of the issues. However, whereas the CPB phase of cardiac surgery lasts a few hours, ECMO support for cardiorespiratory failure may run for days or weeks. The majority of pharmacokinetic studies during CPB are therefore not at steady-state conditions, making it difficult to extrapolate results to ECMO. The overall paucity of clinical data available on drug disposition in ECMO presents a clinical challenge. Intensivists managing patients during ECMO should have an understanding of the potential effects that extracorporeal circuits may have on the disposition of drugs.

The Mechanics of the ECMO Circuit

A schematic representation of the ECMO circuit is given in Figure 1. Blood siphons from the venous cannula through PVC tubing, driven by the right

arterial pressure and a drop of one metre into a distensible silicone bladder at floor level. A roller pump draws blood from the bladder and pushes it through silicone membrane oxygenators and then a heat exchanger, before returning it to the patient. The bladder and pump are linked by a trip-switch mechanism so that if pump flow exceeds venous drainage, the bladder collapses to inhibit pump flow. Extracorporeal circulation of blood requires continuous systemic heparinisation to prevent thrombus formation in the circuit and membrane oxygenator.

The technique is categorised as either veno-venous (VV) or veno-arterial (VA), depending on the type of cannulation. In VV ECMO, deoxygenated blood is drained and oxygenated blood reinfused via venous sites. In neonates this is achieved by placing a double lumen cannula in the right internal jugular vein. In VA ECMO, deoxygenated blood drawn from the right internal jugular vein is returned oxygenated via the right common carotid artery. While VV ECMO provides support purely with gas exchange, VA ECMO also supports the heart[1].

The Effects of Flow Rates and Injection Sites on Drug Delivery

One of the most fundamental differences between ECMO and non-ECMO patients is the site of drug delivery. The ECMO circuit has multiple ports available for infusion of drugs, blood products, parenteral nutrition, for blood sampling and for attachment of haemofiltration circuits, although the exact location of these ports varies between centres. The method of drug administration during ECMO also varies between centres with no current accepted or published guidelines.

Although it is possible to administer drugs via direct access into the patient, systemic heparinisation necessitates minimal direct interventions, such as intravenous line insertion, in order to avoid excessive bleeding. Drugs administered via an umbilical venous catheter opening at the entrance of the right atrium may be recirculated to the ECMO circuit, though there is probably an element of drug recirculation during VV ECMO anyway. Most drugs are therefore administered directly into the ECMO circuit.

The effects *in vitro* of circuit injection sites and flow rates on the distribution of injected solutions have been studied using isolated ECMO circuits with different sized venous reservoirs (30 ml and 50 ml), minus the membrane oxygenator and heater[4]. A bolus of 0.8 ml of Bordeaux Red, a water-soluble dye, followed by a 3 ml flush, was injected into the circulating fluid at sites proximal, distal and directly into the venous reservoir. Samples taken at varying ECMO flow rates and intervals were analysed for dye concentration. The researchers found that dye injected proximal and directly into the venous reservoir pooled at the top of the reservoir at flow rates of 75 ml/min (a common occurrence during the weaning phase of ECMO). The concentration of dye at the top of the venous reservoir during stagnation was 30 times greater than in the ECMO circuit and this stagnation lasted approximately one hour. Furthermore, the investigators determined that some pooling of dye was possible at flow rates less than 250 ml/min. Dye injected distal to the reservoir did not pool in the venous reservoir at any flow rate studied[4].

These results may be explained by the lack of turbulence at low ECMO flow rates, so that the dye, which has a lower specific gravity, stagnates at the top of the venous reservoir, an area of decreased flow. In fact, the specific gravity of most drugs used clinically is lower than that of blood, and hence pooling may contribute to incomplete drug delivery. Although these results suggest that drug administration distal to the reservoir may be optimal, this site increases the risk of air embolism. Thus many ECMO centres choose to administer drugs proximal to the reservoir, allowing the top of the venous reservoir to serve as an air trap.

Pharmacokinetic and Physiological Changes During ECMO

Haemodilution

The most obvious alteration to pharmacokinetics occurs on initiation of ECMO, when the patient's own blood volume mixes with the priming volume in the extracorporeal circuit. For example, in neonates the effective circulating volume will be at least doubled, to 900 ml, on initiation of ECMO. The immediate effect of this acute haemodilution is a decrease in the total blood concentration of any drug present. The pharmacological impact will depend on the apparent volume of distribution (V_d) of the drug, the degree of protein binding and the extent of equilibration between tissue concentrations and plasma concentrations on initiation of ECMO. Drugs with a large volume of distribution (e.g. fentanyl) would be expected to show only a slight change following the expansion of plasma volume, the initial lowering of plasma concentration from haemodilution being counteracted by the back diffusion of the drug into plasma from the large tissue reservoirs. In contrast, a drug with a small volume of distribution (e.g. gentamicin) may be significantly

affected, since the resultant enlarged apparent V_d may affect the elimination rate of the drug.

The acute haemodilution on initiation of ECMO also produces a large reduction in circulating plasma protein concentration such as albumin and α_1-acid glycoproteins. In the blood, drugs exist as free (unbound) drug in equilibrium with protein-bound drug, and it is the free drug that interacts with the receptor to exert a pharmacological effect. For drugs that are highly protein bound, the decreased concentration of binding proteins will lead to an increase in the fraction of unbound drug. This may favour transfer of drug from the plasma to the tissues and thus contribute to the lowering of plasma concentration. The pharmacodynamic result of this may be an increased effect because of an increased free fraction at the receptor site. This, however, would be a transient effect, as following cannulation it is standard practice in ECMO to normalise the effects of haemodilution by transfusing blood and related products, including albumin.

The effects of continuous heparin administration on plasma protein binding may also be of importance. In addition to displacing drugs bound to proteins, heparin may induce the release of lipoprotein lipase and hepatic lipase, increasing the plasma concentration of free fatty acids, which may displace drugs from protein binding sites and increase free drug levels with resultant enhanced pharmacological effect.

The immediate effects on plasma concentration of haemodilution only (disregarding changes in protein binding effects) may be described by the formula[5]:

$$\Delta C_p = \frac{C_p \times V_c}{(V_1 + V_c)}$$

where ΔC_p = Change in drug concentration
C_p = Plasma concentration prior to haemodilution
V_c = Volume of circuit
V_1 = Volume of distribution of the central compartment

The Effects of Haemodilution and Protein Binding Changes on Drugs Administered During ECMO

The expanded circulating volume should not significantly affect drugs with a high V_d and low protein binding administered during ECMO. However, it is possible that the properties that confer a higher V_d (e.g. lipid solubility) may result in greater interactions with the circuit. A drug with a low V_d administered during ECMO will tend to have a lower initial plasma concentration owing to the dilution effect, and its elimination rate may be significantly affected. A drug with high plasma protein binding may have a higher effective (free drug) plasma fraction (because of decreased protein binding) through heparin displacement and hence greater distribution into tissues, resulting in a higher apparent V_d.

Changes in Physiology and Blood Flow

Anderson et al.[6] noted an initial increase in bodyweight of between 5% and 30% in neonates with severe respiratory failure post-cannulation for ECMO. They attributed this increase to the initial resuscitation prior to cannulation and intrinsic increases in intracellular and extracellular water. Such a fluid expansion could significantly affect the volume of distribution of many water-soluble drugs. Furthermore, many ECMO patients will require haemofiltration in an effort to diurese to dry weight and improve lung function. Although haemofiltration improves outcome, it adds uncertainty to the pharmacokinetics of drugs.

Whereas VV ECMO results in pulsatile blood flow, VA ECMO at high flow rates (> 100 ml/kg/min) may produce non-pulsatile flow. Non-pulsatile blood flow can alter perfusion of tissues, reducing capillary circulation and aerobic metabolism[7]. Under experimental conditions, pulseless perfusion of the kidneys of dogs resulted in reduced urine production and impaired sodium excretion, although glomerular filtration was not affected[8]. The kidneys interpret pulseless blood flow as hypotension and activate the renin–angiotensin system[9]. Regional blood flow changes in the liver can also affect drug clearance, in particular those drugs with a high extraction ratio, e.g. propranolol, lignocaine.

Perfusion of tissues may also be altered as a result of activation of the systemic inflammatory response syndrome releasing a variety of autonomic, endocrine and local cytokine reflexes that may affect not only tissue distribution of drugs, but probably also clearance mechanisms as well[10].

Sequestration of Drugs by the ECMO Circuit

Reduced bioavailability of drugs as a result of interactions with plastics is a well-recognised phenomenon. For example, drugs such as insulin, glyceryl trinitrate and diazepam are known to bind to polyvinyl chloride (PVC) infusion bags, administration sets and filters[11]. The potency loss appears to be a function of drug concentration and infusion time. It has also been shown that the

Table 1. Drugs Sequestered by ECMO Circuit

Drug	References	Component tested			Octanol–water partition coefficient*
		Circuit	PVC tubing	Silicone membrane oxygenator	
Morphine sulphate	32	–	✔	✖	6.03
	30	✔	–	–	
Lorazepam	31	–	✔	✔	324
Midazolam hydrochloride	31, 32	–	✔	✔	–
Diazepam	31	–	✔	✔	631
Propofol	31	–	✔	✔	6166
Phenytoin sodium	30	✔	–	–	High
Phenobarbitone sodium	29	–	✔	✖	60
	30	✔	–	–	
Gentamicin sulphate	30	✔	–	–	Low
Vancomycin hydrochloride	30	✔	–	–	Low

✔ = Sequestered; ✖ = Not sequestered; *Data from Lund 1994, Reference 61

opposite effect, leaching of phthalate plasticisers into the solution, may occur[12]. Much of the work investigating drug uptake by extracorporeal circuits has been carried out as experiments *in vitro* in cardiopulmonary bypass circuits. These report significant sequestration of opioids (alfentanil, fentanyl, morphine), benzodiazepines (midazolam, diazepam, lorazepam), glyceryl nitrate and propofol[13–24]. Factors affecting the degree of uptake include the physico-chemical characteristics of the drug, the design of the oxygenator and nature of the priming solution[25–28]. The octanol/water partition coefficient is a measure of a chemical compound's affinity for the organic or aqueous phase, or distribution between the two. Thus compounds with a high ratio will be very soluble in organic materials such as plastics and can be expected to exhibit considerable loss in an ECMO circuit. The oxygenator with the greatest capacity for binding is the silicone membrane oxygenator (e.g. Avecor Cardiovascular Inc, Plymouth, MA, USA)[26]. Furthermore, reversibility of this binding by the oxygenator is related to the drug's protein-binding characteristics, lipophilic drugs that are more highly protein bound displaying more reversibility. The majority of CPB oxygenators currently available on the market today are polypropylene based. They have a microporous structure in a microtubular or sheet design and appear to sequester drugs to a much lesser degree[26].

The component materials of an ECMO circuit are very similar to the CPB circuit. The circuit tubing is composed of PVC while the oxygenator used in ECMO is the Avecor silicone membrane construction. It is therefore perfectly plausible that both of these components will lend themselves heavily to drug adsorption and hence reduce bioavailability, since the patient's blood is continuously exposed to a large surface area during ECMO. Comparatively fewer investigations *in vitro* have been conducted in ECMO circuits, although similar investigations have revealed significant drug uptake of benzodiazepines, propofol, phenobarbitone and morphine (Table 1)[29–32].

The clinical significance of sequestration of drugs has been difficult to interpret. A susceptible drug administered as a bolus dose may result in an attenuation of the expected plasma concentration. This is likely to be a first-order process, i.e. uptake by the circuit is proportional to the circulating concentration. The rate of uptake into the plastic is thought to be an equilibrium process between the mobile phase (blood) and the plastic components, although true equilibrium will not be attained in a flowing circuit. Thus, the level of drug reaching the patient will be at some intermediate concentration between that injected and the steady-state equilibrium value. In a drug with a small volume of distribution, the pharmacological impact of the decrease in plasma concentration will depend on the effect this will have on the concentration at the receptor site. Drugs with a large volume of distribution may be less affected since any drug removed by the circuit will be replaced by the large tissue reservoirs.

The impact of this phenomenon may also be different in CPB compared to ECMO because the two processes differ in terms of time span. For

example, uptake of drugs is assumed to be a saturable process with continuous administration resulting in increased plasma/tissue concentrations and/or clearance. It has been estimated that the circuit components have a large capacity to sequester drugs, so that with most drugs saturation point is only likely to be reached during prolonged administration, and therefore only in ECMO. Furthermore, in an ECMO circuit that has been used for several days, it is possible that once infusion of drug ceases the drug sequestered by the plastic will be liberated back into the circulating blood and unexpectedly prolong the pharmacological effect. In fact it is also conceivable that the metabolite of parent drugs or another co-administered drug has a higher affinity for circuit binding sites and may be able to displace the parent drug.

The Effect of ECMO on the Disposition of Specific Drugs

Opioids

Haemodilution

Although opioids are extensively used in infants during ECMO, very few studies have investigated their disposition. In contrast, the disposition of opioids (apart from morphine) during CPB has been extensively reported[33–40]. Studies of single large bolus doses of fentanyl (60–75 microgram/kg), administered at induction of anaesthesia to adult cardiac surgical patients, have demonstrated reductions in plasma concentrations of fentanyl of between 30% and 60% of pre-CPB concentrations within minutes of the onset of CPB. This decrease was greater than that which could be attributed to haemodilution alone. The concentration of fentanyl remained stable during CPB. In these studies, bubble oxygenators, crystalloid primes and hypothermia to 25–30°C were used[33–35]. Studies investigating the continuous infusions of fentanyl, started before CPB, at an initial high rate (30–50 microgram/kg/min) followed by a lower maintenance infusion (0.15–0.5 microgram/kg/min), have demonstrated a smaller decrease (mean 30%) in plasma concentrations at the onset of CPB compared with a single large bolus dose[35–36]. This is presumably because the maintenance of continuous infusion counteracts the initial decrease. Furthermore, during CPB, the concentration of fentanyl returned to near pre-CPB values within 30 minutes.

Sequestration

Investigations *in vitro* have demonstrated significant sequestration of fentanyl by components of the circuits[13–17]. Addition of fentanyl to the prime was shown to prevent the initial decrease in plasma concentration at the initiation of bypass, but after 2.5 minutes similar concentrations to those measured without the addition of prime were recorded[16]. A decrease in concentration of 68% was observed after the first pass through a membrane oxygenator[14]. Loss of fentanyl was greater at high pH, suggesting lipophilic binding to the circuit[15]. The use of bubble or membrane oxygenators, or blood or crystalloid solutions for priming, did not appear to influence the degree of sequestration, although a subsequent study revealed that the type of membrane oxygenator does[16,25].

In contrast to fentanyl, studies investigating the sequestration of alfentanil to bypass circuitry have shown zero or minimal loss using both membrane and bubble oxygenators[15,16]. In fact, free alfentanil concentrations have been shown to remain relatively constant throughout CPB, as a result of an increase in the unbound fraction. The decrease in total alfentanil concentrations was explained by a dilution of α_1-acid glycoprotein[38,40]. This data illustrates that is important to measure the active free concentrations of the drug.

In a retrospective review of 37 newborn infants on ECMO, unexpectedly large doses of fentanyl to achieve adequate sedation were reported, with the infusion rate of fentanyl increasing with length of time on ECMO. Withdrawal symptoms were observed in 57% of the neonates, duration of ECMO being the most powerful predictor. In the same study, the continuous infusion doses of fentanyl were correlated with plasma fentanyl concentrations in five neonates. Plasma concentrations climbed steadily during the period of infusion, suggesting the development of tolerance to the sedating effects and possibly explaining the large doses administered. The authors suggest that if binding to the ECMO circuit was the reason for the increased dosing requirements, the dose would have decreased over time as the membrane oxygenator became saturated[41].

In another prospective study, plasma levels of fentanyl were analysed in 12 infants undergoing VA ECMO who received a bolus dose followed by an infusion. Plasma levels were taken 6 h following the fentanyl bolus. This time lag was chosen as the researchers felt that this would ensure the membrane oxygenator would reach saturation. Adequate sedation was achieved in all neonates with continuous infusion doses not exceeding 7 microgram/kg/h. Overall, there was no correlation between the plasma fentanyl levels and either the time on ECMO or the fentanyl infusion rate. The plasma levels generally

Table 2. Summary of mean pharmacokinetic values obtained in neonatal ECMO patients					
Drug	**References**		**V_d (litre/kg)**	**Cl^- (litre/kg/h)**	**$t_{½}$ (h)**
Morphine	43	*on ECMO	–	0.57 (0.3)	–
		off ECMO	–	1.06 (0.73)	–
	44			0.70 (0.56)	
Gentamicin	53		0.51 (0.11)	0.05 (0.03)	9.5 (4.2)
	54	*on ECMO	0.58 (0.04)	0.04 (0.003)	10.0 (0.7)
		off ECMO	0.45 (0.02)	0.06 (0.004)	5.7 (0.4)
	55		0.62 (0.25)	0.08 (0.03)	7.6 (5.3)
	56		0.67 (0.15)	0.05 (0.02)	10.4 (3.0)
	57 (median values)	*on ECMO	0.75	0.24 litre/h	9.24
		off ECMO	0.47	0.35 litre/h	3.87
	58	*on ECMO	0.76 (0.3)	0.04 (0.01)	12.65 (4.16)
		off ECMO	0.42 (0.03)	0.04 (0.001)	8.31 (0.87)
Vancomycin	59		0.68 (0.12)	0.066 (0.019)	7.7 (2.6)
	60		1.1 (0.5)	0.047 (0.011)	16.9 (9.5)
	61		0.45 (0.18)	0.039 (0017)	8.3 (2.2)

*Comparison of values obtained during ECMO and after decannulation

increased over the first four days and then tended to decrease thereafter without significant increase in infusion rates[42]. Although not mentioned by the authors, the initial increase in plasma levels on constant infusion may possibly be attributed to circuit saturation, altered hepatic blood flow and redistribution from tissues. Although not clear from the data provided, the decrease in plasma levels beyond day 4 may have been related to the improvements in the patients' hepatic and pulmonary blood flow. The authors attributed the elevations in plasma levels to decreased clearance, and curiously correlated this with renal function despite evidence that fentanyl is primarily cleared via the liver.

Although there has been little work on the effect of CPB on plasma morphine concentrations, there have been two studies *in vivo* and two studies *in vitro* investigating morphine disposition in ECMO (Tables 1 and 2)[30,31,43,44]. In a prospective, comparative study, Dagan et al. investigated morphine pharmacokinetics during and after ECMO[43]. They did not stipulate whether it was VA or VV ECMO, although stated that it was for cardiopulmonary support, implying VA ECMO. Data was collected on seven infants (age range 1 day to 12 months) receiving continuous infusion of morphine between 20 microgram/kg/h and 40 microgram/kg/h. The opioid infusion rate remained unchanged for at least 22 hours during ECMO, and the infusion rate was not changed after decannulation. Blood samples were taken at intervals of 10 h while on ECMO and off ECMO. Mean morphine serum concentrations were found to be twice those taken after ECMO was discontinued. Two of the study infants (neonates aged 1 and 2 days) who recorded the steepest decline in serum morphine concentrations post-ECMO, experienced symptomatology consistent with opioid withdrawal. The calculated clearance of morphine approximately doubled when the infants were taken off ECMO.

The authors suggested that impaired hepatic metabolism and/or hepatic blood flow may be the reason for decreased clearance on ECMO, although there was no clinical evidence of this and no direct measurement of hepatic blood flow was conducted. A renewal of blood flow to the lungs at the end of ECMO, and therefore an increase in V_d causing an initial decrease in the serum concentration, was also suggested as a possible reason. However, this would have been a transient effect and mean steady-state concentrations should return to normal. The researchers conclude that the mechanisms leading to the changes in morphine's disposition are unclear, but it is wise to monitor carefully pharmacological effects on and off ECMO.

In another prospective study by Geiduschek et al., morphine sulphate pharmacokinetics during continuous infusion was determined in 11 neonates with severe persistent pulmonary hypertension and receiving VA ECMO support[44]. All patients received one or two boluses of morphine before commencing an infusion of

10–20 microgram/kg/h. Blood samples were taken at baseline (before the cannulation procedure) and compared with samples obtained from sites immediately proximal and distal to the membrane oxygenator at five minutes, and one and three hours after commencement of ECMO. Morphine clearance was also calculated using paired samples collected on days 1, 3 and 5 of ECMO, beginning at least 12 h after the start of ECMO and any change in morphine infusion rate.

A baseline (pre-ECMO), morphine concentration was only obtained in five patients. No significant decrease in serum morphine concentrations was seen in these five patients on initiation of ECMO. This is somewhat surprising since a decrease in concentration would have been expected owing to the haemodilutional effect. It is possible that since the first sample was not collected until 5 min, the plasma levels had re-equilibrated from tissue stores. Morphine concentrations were also not significantly different in samples obtained simultaneously from sites immediately proximal and distal to the silicone membrane oxygenator (Avecor), suggesting that morphine sulphate does not bind to the membrane oxygenator. Values for clearance were significantly depressed in four patients, although clinical information regarding their hepatic and renal function was not supplied. Three patients in the study had a primary diagnosis of congenital diaphragmatic hernia, although it was not stated if these were included in any of the four patients with depressed clearance. Five patients had increased clearance during ECMO, contradicting the results of the previously discussed study. The authors conclude that the clearance for morphine in patients receiving ECMO is variable and the range of clearance values exceed those published previously for infants who are receiving morphine infusions.

Dagan et al. conducted a preliminary study of the effects *in vitro* of two ECMO circuits (primed with blood) on the disposition of common paediatric drugs[30]. One circuit was new and the other was used clinically for five days. Blood samples drawn from the circuit at 10, 30, 60 and 240 minutes revealed a 36% decrease in the morphine concentration in the new circuit and a lesser decrease of 16% in the used circuit. These results suggest that the process of drug uptake may be influenced by factors such as prior exposure of the circuit.

Benzodiazepines

Haemodilution

The administration of a bolus dose of midazolam (0.15 mg/kg) was found to suffer a decrease in

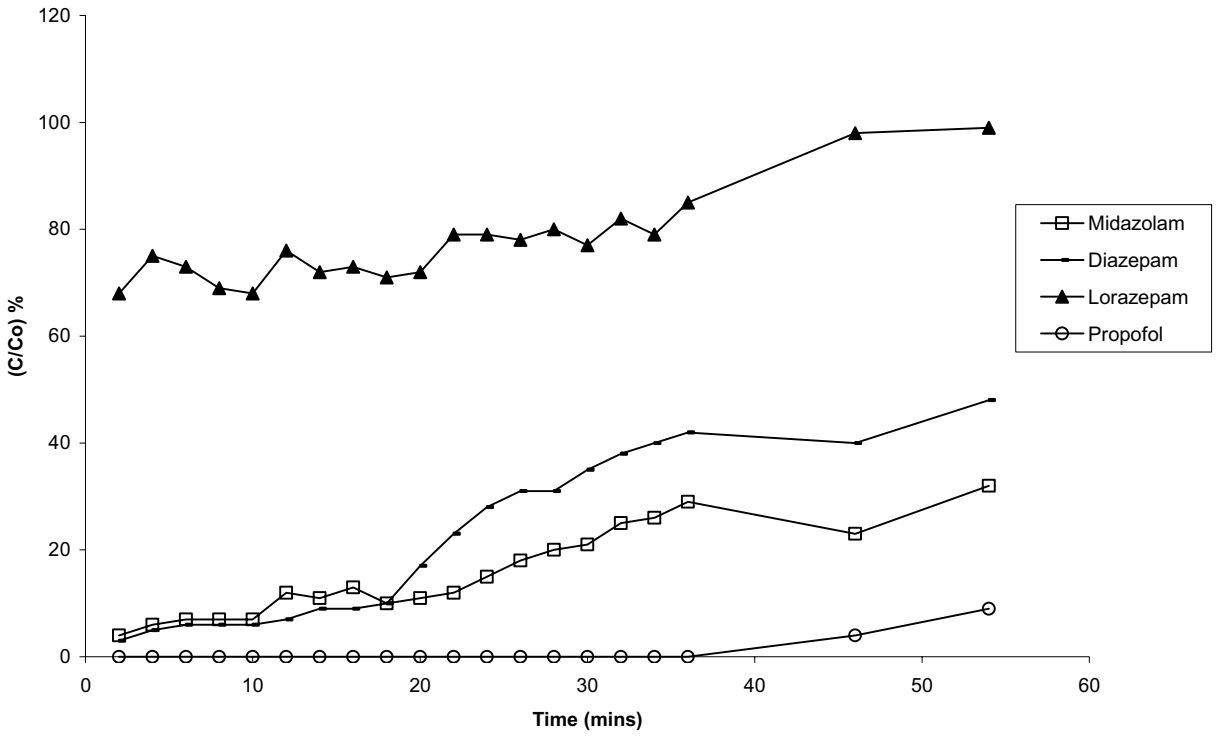

Figure 2. Percentage ratio of the measured concentration (C) and the initial infusion concentration (C0) of the sedative drugs after single passage through an EMCO circuit

concentration on establishing CPB and an increase in concentration post-CPB with a prolonged elimination half-life[45]. Dawson et al. noted that, although the total concentration of midazolam dropped on CPB, the unbound concentration remained stable, and so the unbound fraction had increased from 5.6 ± 1.0% to 11.2%[46]. Similar haemodilutional effects have been observed with lorazepam[47,48].

Sequestration

Mulla et al. evaluated *in vitro* benzodiazepine losses in ECMO circuits after observing that doses of sedative drugs required to achieve desired levels of sedation in ECMO neonates were far greater than those used in non-ECMO patients (Table 1)[31]. The drugs were infused through a complete linear ECMO circuit at the point blood is normally drained from the patient, and the researchers monitored the levels of drugs in the solution post-oxygenator (at the point where blood would be reinfused into the patient). The flow rate of the circuit was set at 350 ml/min and samples were taken at two-minute intervals. The investigation revealed that, in the early stages, the concentration of drugs measured post-oxygenator was considerably lower than anticipated. The data in Figure 2 show the concentration versus time measured post-oxygenator, and expressed as a percentage of the initial infusion concentration. The results clearly show that over the first 40 min of running a non-albumin-treated ECMO circuit, < 50% of the expected level of midazolam and diazepam are transmitted by the ECMO circuit, and as little as 10% of propofol passed through the circuit and was able to reach the patient[31].

In a retrospective comparative analysis of sedative requirements in ECMO and matched post-cardiac surgical neonates, higher doses of morphine and midazolam were required by ECMO neonates to achieve adequate sedation[32]. It was suggested that there is a shift in the sedative dose range requirements such that dose ranges of morphine of 9–70 microgram/kg/h (normal 10–40 microgram/kg/h) and midazolam 112–503 microgram/kg/h (normal 30–200 microgram/kg/h) were required in ECMO patients. Furthermore, significant adsorption of morphine and midazolam to the PVC circuit tubing and silicone oxygenator membrane was revealed. These results suggest that circuit interactions may affect the bioavailability of these drugs and hence the doses required to induce a therapeutic effect.

Propofol

Although the therapeutic use of propofol in paediatric or adult ECMO has not been described, it has been widely studied in the context of CPB, with conflicting results[46,49–51]. In two studies, the initiation of bypass, when propofol was being administered as a continuous infusion of 3–6 mg/kg/h, resulted in a decrease in total concentration of 50–78%[49,51]. A corresponding increase in free fraction and free concentration was demonstrated, probably from haemodilution. In another study, no change in total concentration of propofol was observed[50].

Propofol is a highly lipophilic and protein bound drug and would therefore be expected to be significantly sequestered by the extracorporeal circuit. In an evaluation *in vitro* of propofol interactions with closed CPB circuits, Hynynen et al. reported that at 5 and 120 minutes after addition of propofol into the circulating solution, only 65% and 25%, respectively, of the predicted levels were measurable in the solution[24]. Hammaren *et al*. demonstrated that priming CPB circuits with heparin did not prevent loss of propofol during tests *in vitro*[28]. Although no studies *in vivo* of propofol in ECMO have been reported, an investigation *in vitro* revealed similar results to CPB circuits (Figure 2)[31].

Anticonvulsants

Marx et al. evaluated the interaction of phenobarbitone with the ECMO circuit, prompted by a retrospective chart review of 20 neonates on ECMO, which showed that twice the normal doses were required to maintain therapeutic drug concentrations[29]. However, specific doses and serum concentration data were not revealed.

The evaluation *in vitro* of phenobarbitone interactions from three repeat investigations revealed mixed results. In two of the three experiments, phenobarbitone concentrations were within 90% of expected values. However, the third circuit had only 47% of the expected level. Furthermore, the researchers were able to extract the sequestered phenobarbitone from the circuit using methanol.

Dagan et al. have also demonstrated *in vitro* similar uptake of phenobarbitone and phenytoin in ECMO circuits[30]. This may explain an increased V_d for phenobarbitone observed in a neonate on ECMO[52].

Glyceryl Trinitrate (GTN)

GTN may be administered during ECMO to treat hypertension and/or to prevent cardiac ischaemia. It is possible, however, that

bioavailability is reduced since there is substantial loss to the circuit and oxygenators[21–23]. This is anticipated since the drug is known to be absorbed by several plastics[11].

Antibiotics

Gentamicin

Gentamicin pharmacokinetics have been widely studied in ECMO with varying results (Table 2)[53–57]. Although an increase in V_d is hypothesised, results from three studies did not support this[53–55]. However, prolonged half-lives and clearance were demonstrated in two of these studies[53–54]. The authors recommended increasing the dosing intervals in neonates on ECMO to 18–24 h. A fourth study compared gentamicin pharmacokinetics in neonates who continued on gentamicin after coming off ECMO[56]. They reported a decrease in V_d after cessation of ECMO and suggested that a loading dose was required to attain appropriate therapeutic levels. In a fifth study by Dodge et al., data from 11 neonates who received gentamicin on ECMO, including six infants who received gentamicin both on and off ECMO, was presented[57]. For six infants, while on ECMO their median V_d was 0.748 litre/kg, considerably greater than the median V_d of 0.47 litre/kg after ECMO was discontinued. Clearance was also shown to be reduced while on ECMO (median 0.239 litre/h vs. 0.350 litre/h). Similarly, half-life was a median 9.24 h on ECMO compared with 3.87 h when off ECMO. The range of target peak and trough plasma levels recommended by all the groups was 5–8 microgram/ml and < 2.0 microgram/ml, respectively.

The local experience in our own institution has been similar, i.e. neonates undergoing ECMO have a higher V_d, lower clearance and a prolonged half-life. To achieve consistent therapeutic levels (peak 5–8 mg/l, trough < 2 mg/l), we recommend an initial loading dose of 3.5 mg/kg followed by a maintenance dose of 2.5 mg/kg once daily. The observed pharmacokinetic effects may not be simply due to the extra circulating volume, but also due to the expanded ECF, non-pulsatile renal blood flow, increased renin and atrial natriuretic peptide release[57]. Furthermore, gentamicin sequestration by the circuit has also been reported[30].

Vancomycin

Vancomycin pharmacokinetics during neonatal ECMO has also been described (Table 2)[58–60]. In an initial prospective study involving six neonates, vancomycin 15 mg/kg was administered every 12 h over 30–60 min. Mean serum concentrations were peak 27.1 ± 6.6 microgram/ml and trough 9.3 ± 5.6 microgram/ml. One- or two-compartment models were fitted to serum values for each patient, revealing an elimination half-life of 7.71 ± 2.61 h, V_d of 0.68 ± 0.12 litre/kg, and clearance 0.066 (0.019) litre/kg/h. The authors compared their data with those of previous studies and concluded that vancomycin pharmacokinetics were no different from non-ECMO neonates. However, despite this conclusion, they changed their dosage for neonates on ECMO to 20 mg/kg every 18 h. In a second prospective trial of 12 neonates, an initial dosage based on gestational age, 15 mg/kg or 20 mg/kg was administered over one hour at intervals of 8, 12 or 18 hours[59]. Pharmacokinetic calculations based on a two-compartment model revealed a V_d of 1.1 ± 0.5 litre/kg, half-life 16.9 ± 9.5 h and clearance 0.047 (0.011) litre/kg/h. Based on these data, the authors recommended a dosage of 20 mg/kg every 24 h.

In the final study reported to date, a retrospective study was conducted in 15 neonates who received vancomycin during ECMO and compared pharmacokinetic values with matched controls[60]. The most frequent regimen administered in both groups was 10 mg/kg every 8 h, producing peak and trough concentrations of 27.5 ± 4.3 and 13.7 ± 2.7 microgram/ml, and 23 ± 5.4 and 13.2 ± 4.5 microgram/ml, respectively. The data was analysed using a one-compartment model revealing a V_d of 0.45 ± 0.18 litre/kg, half-life of 8.29 ± 2.23 h, and clearance of 0.039 litre/kg/h in ECMO neonates. The parameters were not significantly different in the control group but the half-life was shorter (6.53 ± 2.05 h, $p = 0.02$). The author recommended that empiric vancomycin regimens incorporate a longer dosing interval than the 6–8 h commonly recommended for term infants. The possible reasons for change in disposition of vancomycin on ECMO may be the same as those affecting gentamicin.

Summary and Conclusions

Critically ill children on ECMO receive a myriad of pharmacological agents. Alterations in drug disposition during ECMO have been reported by a number of workers. The disposition of these drugs during ECMO is a complex issue with the interplay of many factors: haemodilution, protein binding changes, changes in physiology (hepatic and renal function), sequestration of drugs by components of the circuit and the influence of injection sites and flow rates.

It is not surprising that disposition of drugs may be affected if one considers the mechanics of

ECMO and resultant changes in physiology. Though considerable work has been carried out in CPB, there are still significant deficiencies in our knowledge because many of the studies have, as yet, been conducted in isolation. Control of significant factors such as pH, temperature, protein content and composition of circuits, has not always been achieved. This is necessary in order to define a model for predicting drug interactions in the extracorporeal circuits. Furthermore, many of the pharmacokinetic changes studied during CPB have been hampered by the short time period on bypass, at most a few hours. Pharmacokinetic analysis is often best conducted under steady-state conditions, which for most drugs will not be reached during bypass. Moreover, pharmacokinetic evaluation and modelling assumes that the physiological processes remain fairly constant during the study period, which is certainly not the case during CPB. Therefore only limited conclusions may be drawn from observations made during CPB, and cannot necessarily be extrapolated to ECMO. It is also important to draw a distinction between the likely effects on disposition of drugs administered prior to ECMO (bolus and continuous infusion), where the initial effects of haemodilution and protein binding changes may be greater, and those administered during ECMO where sequestration of drugs and altered hepatic and renal blood flow may play a greater role.

Consistent and predictable drug delivery helps to ensure optimal paediatric care, improving the prospects of recovery. Although literature in ECMO has become extensive in recent years, studies and discussions regarding pharmacotherapy remain scanty. Taking into consideration the potential changes in drug delivery that can occur during ECMO, coupled with the fact that pharmacokinetic changes are likely in critically ill neonates, drug regimens should be individualised through therapeutic drug monitoring whenever possible. Clinicians must be particularly vigilant in assessing for therapeutic and adverse effects.

References

1. Bartlett RH, Roloff DW, Custer JR, Younger JG, Hirschl RB. Extracorporeal life support: The University of Michigan Experience. JAMA 2000;283:904-8
2. ECMO trial group. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. Lancet 1996;348:75-81
3. Peek GJ, Killer H, Sosnowski AW, Firmin RK. Extracorporeal membrane oxygenation: potential for adults and children? (Review). Hospital Medicine (London) 1998;59:304-8
4. Hoie E et al. Effects of injection site and flow rate on the distribution of injected solutions in an extracorporeal membrane oxygenation circuit. Am J Hosp Pharm 1993;50:1902-6
5. Mets B. The pharmacokinetics of anaesthetic drugs and adjuvants during cardiopulmonary bypass. Acta Anaesthesiol Scand 2000;44:261-73
6. Anderson HL, Coran AG, Drongowski RA, Ha HJ, Bartlett RH. Extracellular fluid and total body water changes in neonates undergoing extracorporeal membrane oxygenation. J Ped Surg 1992;27:1003-8
7. Shevde K, Dubois WJ. Pro: Pulsatile flow is preferable to non-pulsatile flow during cardiopulmonary bypass. J Cardiothorac Anesth 1987;1:165-8
8. Many M, Soroff SH, Birtwell WC, Wise HM, Deterling RA. The physiologic role of pulsatile and nonpulsatile blood flow. Arch Surg 1968;97:917-23
9. Bartlett RH. Extracorporeal life support for cardiopulmonary failure. Curr Probl Surg 1990;27:621-705
10. Gravlee GP, Davis R, Kurusz M, Utley JR. Cardiopulmonary Bypass: Principles and Practice. Philadelphia; London: Lippincott Williams and Wilkins, 2000, p. 265
11. Trissel LA. Handbook on Injectable Drugs, American Society of Health-System Pharmacists, 10th edn, 1998: XI
12. Karle VA, Short BL, Martin GR et al. Extracorporeal membrane oxygenation exposes infants to the plasticizer, di(2-ethyl hexyl)phthalate. Crit Care Med 1997;25:696-703
13. Koren G, Crean P, Klein J, Goresky G, Villamater J, MacLeod SM. Sequestration of fentanyl by the cardiopulmonary bypass (CPBP). Eur J Clin Pharmacol 1984;27:51-6
14. Rosen DA, Rosen KR, Davidson B, Nahrwold ML, Broadman L. Absorption of fentanyl by the membrane oxygenator. Anesthesiology 1985;63:A281
15. Skacel M, Knott C, Reynolds F, Aps C. Extracorporeal circuit sequestration of fentanyl and alfentanil. Br J Anaesth 1986;58:947-9
16. Hynynen M. Binding of fentanyl and alfentanil to the extracorporeal circuit. Acta Anaesthesiol Scand 1987;31:706-10
17. Rosen D, Rosen K, Davidson B, Broadman L. Fentanyl uptake by the Scimed Membrane Oxygenator. J Cardiothorac Anesth 1988;2:619-26
18. Rosen D, Rosen K, Leong P. Uptake of lorazepam and midazolam by the Scimed membrane oxygenator. Anesthesiology 1988;73:A474
19. Silvasi DL, Rosen DA, Rosen KR. Absorption of midazolam by the Scimed membrane oxygenator. Anesth Analg 1989;68:S261
20. Keaveny J, Clarke C, Pleuvry B, Whittaker DK. Midazolam levels in the isolated cardiopulmonary bypass circuit. Anesth Analg 1991;72:S133
21. Dasta JF, Jacobi J, Wu LS et al. Loss of nitroglycerin to cardiopulmonary bypass apparatus. Crit Care Med 1983;11(1):50-52
22. Dasta JF, Weber RJ, Wu LS et al. Influence of cardiopulmonary bypass on nitroglycerin clearance. J Clin Pharmacol 1986;26:165-8
23. Booth BP, Henderson M, Milne B et al. Sequestration of glyceryl trinitrate (nitroglycerin) by cardiopulmonary bypass oxygenators. Anesth Analg 1991;72:493-7
24. Hynynen M, Hammaren E, Rosenberg PH. Propofol sequestration within the extracorporeal circuit. Can J Anaesth 1994;41:583-8
25. Rosen KR, Rosen DA, Silvasi DL. Factors which affect midazolam uptake by the Scimed membrane oxygenator. Anesth Analg 1989;68:S238

26. Rosen DA, Rosen KR, Silvasi DL. In vitro variability in fentanyl absorption by the different membrane oxygenators. J Cardiothorac Anesth 1990;4:332-5
27. Su HB, Tseng CC, Jenn CT, Chang CL, Huang JD. Changes of propofol levels in isolated cardiopulmonary bypass circuit. Acta Anaesthesiol Sin 1996;34:17-20
28. Hammaren E, Rosenberg PH, Hynynen M. Coating of extracorporeal circuit with heparin does not prevent sequestration of propofol in vitro. Br J Anaesth 1999;82:38-40
29. Marx CM, Litmanovitz I, Ksenich R, Cornell DJ, Walsh-Sukys M. Investigation of increased phenobarbital dose requirement for newborn infants on ECMO: in vitro adsorption to ECMO circuit. Pharmacother 1991;11:270
30. Dagan O, Klein J, Gruenwald C, Bohn D, Barker G, Koren G. Preliminary studies of the effects of extracorporeal membrane oxygenator on the disposition of common pediatric drugs. Ther Drug Monit 1993;15:263-6
31. Mulla H, Lawson G, von Anrep C et al. In vitro evaluation of sedative drug losses during extracorporeal membrane oxygenation. Perfusion 2000;15:21-6
32. Mulla H, Lawson G, Woodland E et al. Neonatal ECMO affects drug disposition. Curr Ther Res 2000;61:838-48
33. Lunn JK, Stanley TH, Eisele J et al. High dose fentanyl anaesthesia for coronary artery surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. Anesth Analg 1979;58:390-95
34. Bovill JG, Sebel PS. Pharmacokinetics of high dose fentanyl. A study in patients undergoing cardiac surgery. Br J Anaesth 1980;52:795-801
35. Hug CC, Moldenhauer CC. Pharmacokinetics and dynamics of fentanyl infusions in cardiac surgical patients. Anesthesiology 1982;57:A45
36. Sprigge JS, Wynands JE, Whalley DG et al. Fentanyl infusion anesthesia for aortocoronary bypass surgery: plasma levels and hemodynamic response. Anesth Analg 1982;61:972-8
37. Koren G, Goresky G, Crean P et al. Pediatric fentanyl dosing based on pharmacokinetics during cardiac surgery. Anesth Analg 1984;63:577-82
38. Kumar K, Crankshaw DP, Morgan DJ, Beemer GH. The effect of cardiopulmonary bypass on plasma protein binding of alfentanil. Eur J Clin Pharmacol 1988;35:47-52
39. Robbins GR, Wynands JE, Whalley DG et al. Pharmacokinetics of alfentanil and clinical responses after cardiac surgery. Can J Anesth 1990;37:52-7
40. Hug CC, Burm AGL, de Lange S. Alfentanil pharmacokinetics in cardiac surgical patients. Anesth Analg 1994;78:231-9
41. Arnold JH, Truog RD, Scavone JM, Fenton T. Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. J Pediatr 1991;119:639-43
42. Leuschen MP, Willett LD, Hoie EB et al. Plasma fentanyl levels in infants undergoing extracorporeal membrane oxygenation. J Thorac Cardiovasc Surg 1993;105:885-91
43. Dagan O, Klein J, Bohn D, Koren G. Effects of extracorporeal membrane oxygenation on morphine pharmacokinetics in infants. Crit Care Med 1994;22:1099-101
44. Geiduschek JM, Lynn AM, Bratton SL et al. Morphine pharmacokinetics during continuous infusion of morphine sulfate for infants receiving extracorporeal membrane oxygenation. Crit Care Med 1997;25:360-64
45. Kanto J, Himberg J, Heikkila H, Arola M, Jalonen J, Laasonen V. Midazolam kinetics before, during and after cardiopulmonary bypass surgery. Int J Clin Pharmacol Res 1985;2:123-6
46. Dawson PJ, Bjorksten AR, Blake DW et al. The effects of cardiopulmonary bypass on total and unbound plasma concentrations of propofol and midazolam. J Cardiothorac Vasc Anesth 1997;11:556-61
47. Boscoe M, Dawling S, Thompson M, Jones R. Lorazepam in open-heart surgery – plasma concentrations before, during and after bypass following different dose regimens. Anaesth Intensive Care 1984;12:9-13
48. Aaltonen L, Kanto J, Arola M, Iisalo E, Pakkanen A. Effect of age and cardiopulmonary bypass on the pharmacokinetics of lorazepam. Acta Pharmacol Toxicol 1982;51:126-31
49. Russell G, Wright E, Fox M et al. Propofol–alfentanil anaesthesia for coronary artery surgery and cardiopulmonary bypass. Anaesthesia 1989;44:205-8
50. Massey NJA, Sherry KM, Oldroyd S, Peacock JE. Pharmacokinetics of an infusion of propofol during cardiac surgery. Br J Anaesth 1990;65:475-9
51. Hammaren E, Yli-Hankala A, Rosenberg PH, Hynynen M. Cardiopulmonary bypass induced changes in plasma concentrations of propofol and in auditory evoked potentials. Br J Anaesth 1996;77:360-64
52. Elliott E, Buck ML. Phenobarbital dosing and pharmacokinetics in a neonate receiving extracorporeal membrane oxygenation. Ann of Pharmacother 1999;33:419-22
53. Southgate MW, DiPiro JT, Robertson AF. Pharmacokinetics of gentamicin in neonates on extracorporeal membrane oxygenation. Antimicrob Agents Chemother 1989;33:817-9
54. Cohen P, Collart L, Prober CG et al. Gentamicin pharmacokinetics in neonates undergoing extracorporeal oxygenation. Paediatr Infect Dis 1990;9:562-6
55. Munzenberger PJ, Massoud N. Pharmacokinetics of gentamicin in neonatal patients supported with extracorporeal membrane oxygenation. Trans Am Soc Intern Organs 1991;37:16-8
56. Bhatt-Mehta V, Johnson CE, Schumacher RE. Gentamicin pharmacokinetics in term neonates receiving extracorporeal membrane oxygenation. Pharmacother 1992;12:28-32
57. Dodge WF, Jelliffe RW, Zwischenberger JB et al. Population pharmacokinetic models: effect of explicit versus assumed constant serum concentration assay error patterns upon parameter values of gentamicin in infants on and off extracorporeal membrane oxygenation. Ther Drug Monit 1994;16:552-9
58. Hoie EB, Swigart SA, Leuschen MP et al. Vancomycin pharmacokinetics in infants undergoing extracorporeal membrane oxygenation. Clin Pharm. 1990;9:711-5
59. Amaker RD, DiPiro JT, Bhatia J. Pharmacokinetics of vancomycin in critically ill infants undergoing extracorporeal membrane oxygenation. Antimicrob Agents Chemother 1996;40:1139-42
60. Buck ML. Vancomycin pharmacokinetics in neonates receiving extracorporeal membrane oxygenation. Pharmacother 1998;18:1082-6
61. Lund W. The Pharmaceutical Codex: Principles and Practice of Pharmaceuticals. London: The Pharmaceutical Press, 12th edn, 1994