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Direct Cardiac Effects of Coronary Site-directed Thiopental and Its Enantiomers

A Comparison to Propofol in Conscious Sheep

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Background: **Previous evidence from laboratory animal studies indicates that *R*-thiopental has a greater margin of safety than either the more potent *S*-thiopental or the clinically used *rac*-thiopental. Although thiopental can cause cardiovascular depression from direct myocardial effects as well as indirect central nervous system and peripheral effects, no studies have yet determined whether its myocardial effects are enantioselective. A lesser direct effect would provide further evidence supporting *R*-thiopental as a preferred single enantiomer replacement for *rac*-thiopental.**

Methods: **The direct myocardial effects of the thiopental enantiomers were compared to those of *rac*-thiopental and propofol, using a crossover design with small incremental doses infused over 3 min, on separate days, into the left coronary arteries of conscious sheep. Hemodynamic and electrocardiographic measurements were acquired, and serial blood samples were collected during the studies for drug analyses.**

Results: **All three forms of thiopental and propofol produced significant hemodynamic effects consisting of dose-related and rapid-onset decreases in left ventricular dP/dt_{max} and stroke volume, and increases in left coronary blood flow and heart rate. Cardiac output, mean arterial blood pressure, and central venous pressure remained unaltered. The effects did not differ significantly among *rac*-thiopental, enantiopure *R*- or *S*-thiopental, or propofol. Arterial blood drug concentrations were consistently less than those associated with systemic effects.**

Conclusions: **Although previous evidence indicates that *R*-thiopental could make a suitable single-enantiomer replacement for *rac*-thiopental, the current study did not find a significant difference in direct cardiac effects among the thiopental enantiomers, racemate, or propofol.**

THE enantiomers of many racemic drugs differ sufficiently in their potency, side effects, and pharmacokinetics for one enantiomer to be preferred pharmacologically to the other enantiomer or to the racemate. Accordingly, an appreciable number of enantiopure drugs have been introduced to replace racemates originally marketed[1]; examples in anesthesia include dexmedetomidine for medetomidine and levobupivacaine for bupivacaine.

Thiopental is a chiral drug that is produced and used as a racemate (*rac*- or *RS*-thiopental). As judged by studies in laboratory rodents, the thiopental enantiomers have qualitatively similar but quantitatively different central nervous system (CNS) effects.[2] Whereas *S*-thiopental is more potent as an anesthetic, *R*-thiopental has a greater margin of safety.[3] The greater potency of *S*-thiopental seems to be a consequence of its higher potency at enhancing the effects of γ-aminobutyric acid (GABA) at the γ-aminobutyric acid type A ($GABA_A$) receptor.[4] Other evidence suggests that the greater margin of safety of *R*- than *S*-thiopental may be due to *R*-thiopental having a smaller heart:brain distribution ratio, with the heart being the main site of fatal adverse effects.[3] Other studies have indicated that *R*-thiopental might also have a small pharmacokinetic advantage in having a somewhat greater mean total body clearance than *S*-thiopental.[5–7]

Taken together, the available data suggest that enantiopure *R*-thiopental could be pharmacologically preferable to *rac*-thiopental as an intravenous anesthetic, but no studies have yet compared the cardiac depressant effects of racemic thiopentone and its enantiomers. A lesser direct cardiac effect would provide additional evidence supporting *R*-thiopental as a preferred single enantiomer replacement for *rac*-thiopental.

Therefore, the aim of this study was to compare the direct cardiac effects of *rac*-, *R*-, and *S*-thiopental; propofol, which is achiral, was used as a comparator. We used a technique of site-directed coronary arterial injection in previously instrumented conscious sheep that we had developed and validated to study direct *versus* indirect cardiotoxicity of local anesthetic agents.[8] In this way, we could study the direct cardiac responses from small doses of the drugs that were equivalent to those perfusing the heart from an intravenous anesthetic dose but small enough to preclude indirect responses from interaction of the recirculated drug with the CNS.

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Materials and Methods

Experimental Design

The study was approved by the joint Animal Care and Ethics Committee of the Royal North Shore Hospital and the University of Technology, Sydney (Sydney, Australia). Using a crossover design, on separate days, small incremental doses of *rac*-thiopental, *R*-thiopental, *S*-thiopental, and propofol were infused for 3 min into the left coronary arteries of previously prepared conscious sheep. During the studies, hemodynamic and electrocardiographic measurements were continuously acquired, and serial blood samples were collected for drug analyses.

Preparation Procedures

The subjects were nonpregnant Merino first-cross ewes (weight, 43–56 kg; n = 10). During general anesthesia, a left thoracotomy was performed to implant an active redirection transit time flow probe (21 mm Triton 200-306-M; Triton Technology Inc., San Diego, CA) around the pulmonary artery for measurement of cardiac output. A transit-time flow probe (4ss; Transonic System Inc., Ithaca, NY) was placed around the left main coronary artery for measurement of coronary arterial blood flow. A spinal catheter (22-gauge Spinocath®; B. Braun Melsungen AG, Melsungen, Germany) to be used for drug infusion was placed retrograde in the left anterior descending coronary artery (paraconal artery in the sheep) and directed into the left main coronary artery to 1 mm proximal to the left coronary artery bifurcation as seen from its exterior. The position of the catheter tip was validated by fluoroscopy. A pressure transducer catheter (Millar 3-French SPR-52; Millar Instruments Inc., Houston, TX) was placed into the left ventricle through the free wall for measurement of left ventricular pressure. Two pairs of stainless steel electrodes (dorsoventral and craniocaudal positions) were sutured onto the pericardium for recording electrocardiographic signal, and the leads exited toward the dorsal midline. The hemiazygos vein, which drains venous blood from the chest of the sheep, was dissected free and ligated at its ventral (proximal) extremity. A catheter (16-gauge, 70-cm polyurethane, Cavafix®; B. Braun Melsungen AG) was inserted into the hemiazygos vein and the tip advanced 5 cm toward the coronary sinus for blood sampling. The chest was closed layer by layer. Two catheters (16-gauge, 70-cm polyurethane cannulae, Cavafix®), one to be used for measurement of mean arterial blood pressure, the other for arterial blood sampling, were placed into the carotid artery and advanced into the aortic arch, and another was placed in the right atrium *via* the jugular vein for the measurement of central venous pressure. After the neck incision was closed, an intravenous injection of 75 mg carprofen was given. The implanted cannulae were attached to a constant infusion of heparinized saline *via* minimum volume extension sets connected to high-pressure (300 mmHg), low-flow (3 ml/h) restrictor devices using a multiple port block from a pressurized 1-l bag (0.9% saline) with heparin (10,000 U) and flucloxacillin (1 g) added. The subjects were placed (and thereafter maintained) in metabolic crates and were monitored until conscious and standing. Postoperatively, buprenorphine (0.3 mg intravenous) was administered three times per day for the first 2 days and twice per day for the next 2 days. Ten days were allowed for recovery, during which time body temperature, heart rate, respiration rate, capillary refill time, wound appearance, appetite, demeanor, urine production, and bowel movements were monitored.

Drugs and Dosage Protocol

Thiopental sodium (racemate: Pentothal®; Abbott Laboratories, Sydney, Australia) and propofol (Diprivan®; AstraZeneca, Sydney, Australia) were supplied from standard hospital stock. *R*- and *S*-thiopental were prepared and characterized as previously described.[9] Infusions of 15 ml, containing doses of 20, 40, and 80 mg *rac*-, *R*-, and *S*-thiopental or 7.5, 15, and 30 mg propofol, were given at a constant rate over 3 min. These doses represented approximately 2.5, 5, and 10% of typical anesthetic induction intravenous doses of thiopental (approximately 800 mg) and propofol (approximately 300 mg) in the adult sheep. The doses were calculated as 50, 100, and 200% of the approximate amount expected to reach the heart after intravenous administration of a usual induction dose, given the fraction of cardiac output normally flowing through the left main coronary artery to be approximately 5%.

Because commercial *rac*-thiopental is prepared as thiopental sodium containing anhydrous sodium carbonate (60 mg/g) to regulate pH for solubility and to maintain chemical stability, each dose of *rac*-thiopental was prepared with a different concentration of sodium carbonate in saline solution to standardize the conditions to those of the commercial preparation (20 mg dissolved in 24 mg Na_2CO_3/100 ml saline, 40 mg dissolved in 16 mg Na_2CO_3/100 ml saline, 80-mg dose dissolved in saline only). All doses of the thiopental enantiomers were prepared with 32 mg Na_2CO_3/100 ml saline, and the solutions were adjusted, if necessary, to be within pH 10–10.5 as used clinically. The responses to infusion of respective simulated vehicle solutions (thiopental: saline with 32 mg Na_2CO_3/100 ml at pH 10.5; propofol: 10% Intralipid® [Baxter Healthcare, Sydney, Australia]), designated as 0-mg doses of the respective drugs, were also determined in each subject.

Before each study, the subject was placed in a sling to prevent recumbency and to maintain position relative to transducers but to allow it to rest as required. After settling into the environment of the laboratory, the subject was monitored for 5 min to determine predrug

baseline values. Drug was infused over 3 min at a constant rate, and data were acquired for a further 27 min.

Data Acquisition and Processing

Analog signals, consisting of electrocardiogram, mean arterial blood pressure, cardiac output, coronary arterial blood flow, left ventricular pressure, and first derivative of left ventricular pressure (dP/dt), were acquired at 256 Hz by a physiologic monitoring system (System 6; Triton Technology Inc., San Diego, CA), digitally converted (MP100; Biopac Systems Inc., Santa Barbara, CA), and captured using a personal computer. Derived data consisted of heart rate, stroke volume, and maximum positive value of dP/dt (dP/dt_{max}) on a beat-by-beat basis. The electrocardiogram was analyzed for arrhythmias, and measurements were made of the time between beginning of P wave to beginning of Q wave or R wave if no Q wave was present (P- to R-wave interval), time from onset of Q wave to end of T wave (Q- to T-wave interval), time between consecutive R waves (R- to R-wave interval), and width of the QRS complex. Also, the Q- to T-wave interval was corrected for heart rate by dividing it by the square root of the R- to R-wave interval (QTc). Because the drugs produced tachycardia, the frequency of the various arrhythmias was adjusted for both the duration of observation and the prevailing heart rate.

Predrug baseline data in each individual study were averaged and assigned values of 100% for comparison with the subsequent values from the respective drug/vehicle infusion periods. Hemodynamic data were divided into 20-s epochs, and the averages during each epoch were determined. Five consecutive electrocardiographic complexes were examined every 1 min during the baseline period, every 20 s for the first 5 min after the commencement of drug/vehicle infusions and every 5 min for 15 min. The data were analyzed for peak effects (E_{max} or E_{min}, as appropriate). In addition, the sum of effects differences, which are analogous to the areas under curve, to 5 and 15 min (SED_5 and SED_{15}) were determined to account for differences in effect time course.[8]

To measure concentrations of drug recirculated to other tissues, arterial blood samples were collected immediately before drug infusion and then at 1, 2, 3, 4, 5, 10, 15, 20, and 30 min later. Blood samples from a catheter with its tip in the coronary sinus were also collected in a subset of the subjects. Blood drug concentrations were analyzed by high-performance liquid chromatography, chirally for thiopental[9] and achirally for propofol.[10]

Statistical Analysis

Statistix for Windows (version 8; Analytical Software, Tallahassee, FL) was used on a personal computer. Staged data analysis was performed. Whether the drug/vehicle infusion produced a significant effect was determined using the Student one-sample *t* test by comparison of the relevant maximal/minimal values (expressed as percent baseline) to a value of 100%. If a significant effect was found, maximal/minimal effect and SED data

Table 1. Pooled Mean (and 95% Confidence Interval) Values Measured during the Baseline Predrug Periods of Each Study

Variable	*RS*-thiopental	*R*-thiopental	*S*-thiopental	Propofol
Hemodynamic				
Mean arterial blood pressure, mmHg	85 (82–89) n = 27	85 (81–88) n = 25	86 (81–90) n = 25	85 (82–88) n = 30
Cardiac output, l/min	4.6 (4.2–5.0) n = 26	4.9 (4.3–5.4) n = 23	4.8 (4.3–5.2) n = 23	4.5 (4.1–4.8) n = 26
Mean left ventricular pressure, mmHg	103 (98–108) n = 26	105 (101–109) n = 27	104 (99–108) n = 27	103 (98–108) n = 27
Left ventricular dP/dt_{max}, mmHg/s $\times 10^{-3}$*	2.7 (2.6–2.8) n = 27	2.7 (2.6–2.8) n = 27	2.7 (2.6–2.9) n = 27	2.7 (2.6–2.8) n = 27
Stroke volume, ml*	54 (49–59) n = 27	57 (50–64) n = 24	54 (49–58) n = 24	52 (47–57) n = 27
Heart rate, beats/min*	86 (80–92) n = 28	85 (80–90) n = 27	89 (82–96) n = 26	87 (81–92) n = 30
Left coronary arterial blood flow, ml/min*	101 (89–113) n = 30	99 (88–111) n = 26	103 (89–118) n = 26	98 (88–107) n = 30
Electrocardiographic				
PR interval†, ms	115 (110–119) n = 25	115 (110–115) n = 22	111 (107–115) n = 22	115 (110–119) n = 24
QRS width‡, ms	74 (72–77) n = 27	73 (71–75) n = 24	74 (71–76) n = 24	74 (71–76) n = 27
QTc interval§, ms	11.8 (11.5–12.1) n = 27	11.6 (11.3–11.9) n = 24	11.8 (11.5–12.0) n = 24	11.9 (11.6–12.2) n = 27

* These hemodynamic variables had significant changes from predrug baseline values during the drug infusion periods. Electrocardiographic measurements were made of † time between beginning of P wave to beginning of Q wave (or R wave if no Q wave was present); ‡ width of the QRS complex; § Q- to T-wave interval corrected for heart rate by dividing it by the square root of the R- to R-wave interval.

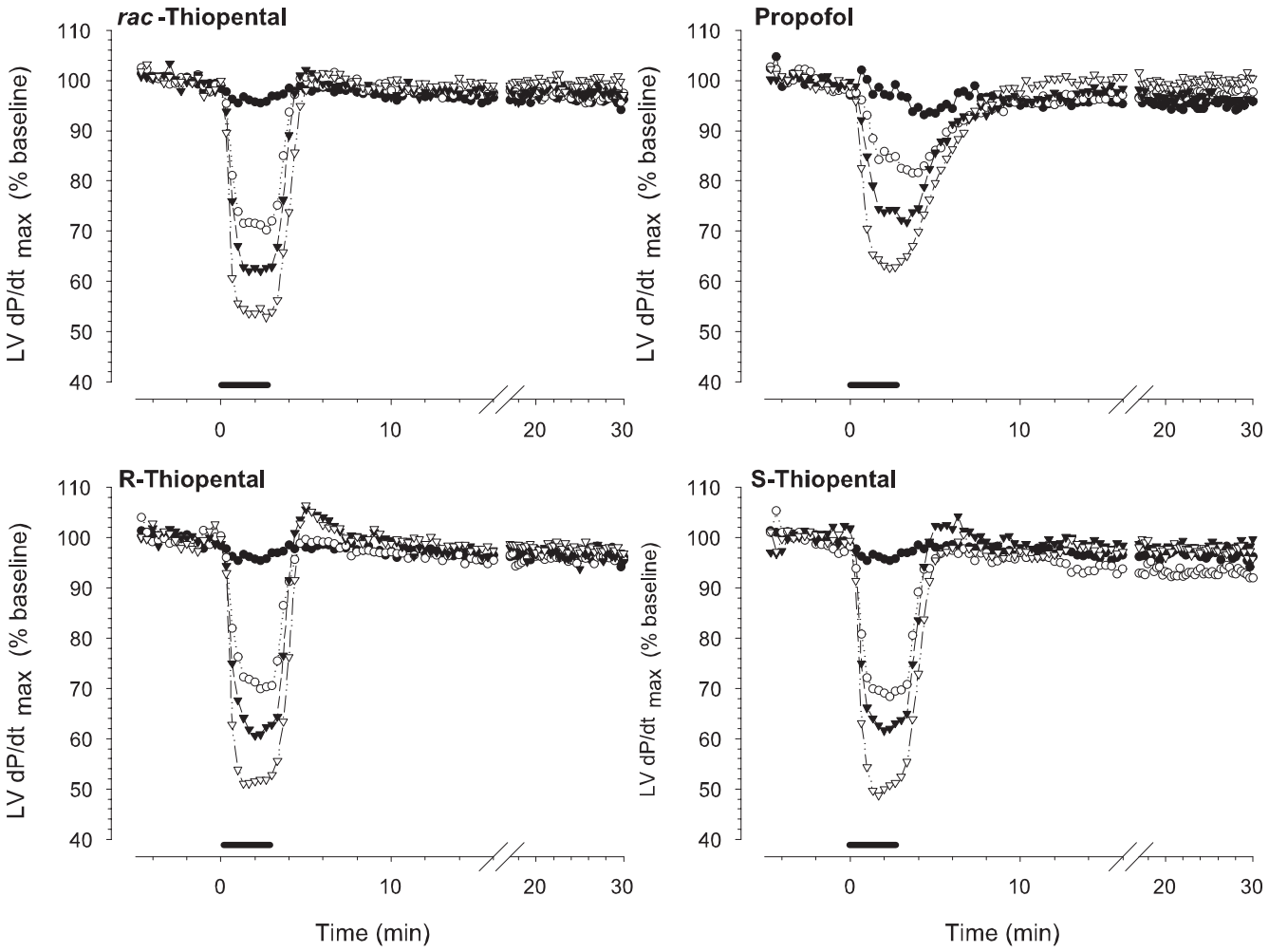

Fig. 1. Time course of mean effects in left ventricular dP/dt_{max} from site-directed left coronary arterial infusions of *rac*-, *R*-, and *S*-thiopental and propofol to conscious adult sheep. Doses in 15 ml were given over 3 min from time 0 at a constant rate: The *horizontal bar* on the time axis indicates the period of drug infusion. Thiopental doses were 0 mg (vehicle; *closed circle*), 20 mg (*open circle*), 40 mg (*closed triangle*), and 80 mg (*open triangle*); those of propofol were 0 mg (vehicle; *closed circle*), 7.5 mg (*open circle*), 15 mg (*closed triangle*), and 30 mg (*open triangle*). Error bars for change have not been shown for clarity of display. Note time scale expansion.

were compared using repeated-measures analysis of variance with drug as a between-subject effect, dose as a within-subject effect, and subject as the repeated measure. A finding of significance was investigated further by *post hoc* testing of differences between mean values using the method of least significant differences and by comparison of mean values for each drug dose to that of the relevant vehicle using the Dunnett procedure. The null hypothesis was equality of the drug effects. A significance criterion of $P < 0.05$ was used. All tests were two tailed. Baseline values of variables are given in table 1 as the pooled mean values and 95% confidence intervals from 22 to 30 individual studies recorded before administration of the three doses of each drug. Changes from the relevant baseline values obtained after drug administration in each individual study are expressed as mean percentage and 95% confidence interval of the respective baseline value before drug administration.

Results

Hemodynamic Effects

All three forms of thiopental and propofol produced significant hemodynamic effects consisting of decreased dP/dt_{max} and stroke volume and increased left coronary blood flow and heart rate, but cardiac output, mean arterial blood pressure, and central venous pressure remained unaltered. Figure 1 shows the time course and magnitude of mean effect on dP/dt_{max} as a function of dose. Changes to dP/dt_{max} and left coronary artery blood flow were extremely rapid in onset, with maximal effects occurring within approximately 1.5 min and with reciprocal maximal changes to heart rate and stroke volume occurring at the end of the 3-min drug infusion period. Figure 2 demonstrates the relative temporal changes for the four main variables at the highest doses of thiopental and propofol; this is representative of the relative time courses found with the other doses. It

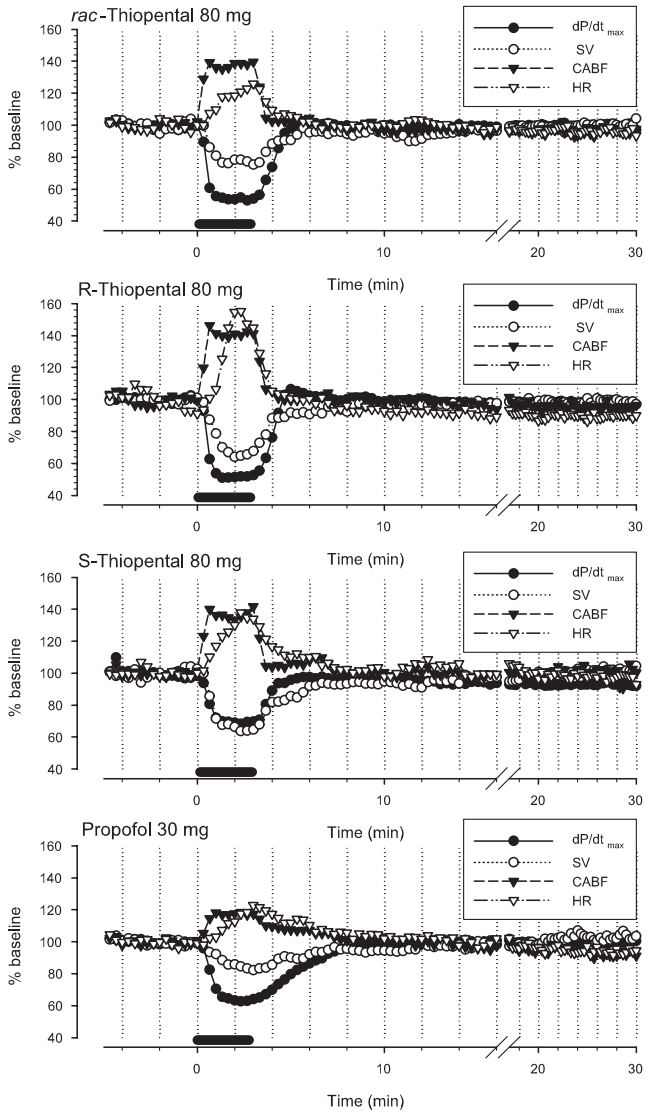

Fig. 2. Time course of mean effects in left ventricular dP/dt_{max}, stroke volume (SV), left coronary artery blood flow (CABF), and heart rate (HR) from site-directed left main coronary arterial infusions of 80 mg *rac*-, *R*-, and *S*-thiopental and 30 mg propofol to conscious adult sheep. Doses in 15 ml were given over 3 min from time 0 at a constant rate: The *horizontal bar* on the time axis indicates the period of drug infusion. Error bars for change have not been shown for clarity of display. Note time scale expansion and the use of time markers to facilitate temporal comparisons.

shows the changes in dP/dt_{max} and left coronary artery blood flow occurring almost immediately, with the changes in heart rate and stroke volume occurring more slowly. The changes from *R*-thiopental occurred and regressed a little faster than those from *S*-thiopental, and changes from all three forms of thiopental consistently regressed faster than those from propofol. Without exception, the changes from all drugs returned to baseline values within 15 min. Although cardiovascular data were collected for 30 min, values beyond 15 min were not included in the subsequent analyses to preclude introduction of experimental noise. There were also small but significant hemodynamic effects of the vehicles for thiopental and propofol. Both maximally decreased dP/dt_{max} and left coronary artery blood flow by approximately 10% ($P < 0.05$), and that for propofol decreased stroke volume and decreased left coronary blood flow by approximately 12% ($P < 0.05$).

The effects of the drugs were dose related and gave essentially parallel dose–response curves for maximal effect (fig. 3), as well as for SED_5 and SED_{15} (fig. 4). Not surprisingly, SED_5 and SED_{15} values were usually similar for thiopental but diverged more for propofol because of its longer duration of effect. Although the maximal effects of propofol tended to be smaller than those of thiopental at the chosen doses, their longer duration produced dose relations as measured by SED_5 and SED_{15} that were similar for thiopental and propofol.

Using the dose potency ratio preselected for the experiments (*rac*-thiopental:propofol = 800:300, based upon equianesthetic doses in sheep), no significant differences between drugs were found for maximal effects on dP/dt_{max} ($P = 0.25$, not significant) or heart rate ($P = 0.18$, not significant). However, the effect of propofol was less on stroke volume ($P < 0.001$) and left coronary artery blood flow ($P = 0.049$). No significant differences between *rac*-thiopental and the separate enantiomers were found for any effect.

Electrocardiographic Effects

No systematic significant effects of any of the drugs was found on P wave–R wave interval or width of the QRS complex. However, the vehicle for propofol increased the width of the P- to R-wave interval by 6%, and both vehicles increased the width of the QRS complex by 6%. Propofol/vehicle did not affect the width of the QTc interval, but all three forms of thiopental increased it ($P = 0.008$: vehicle by 5%, 20 mg by 7%, 40 mg by 11%, 80 mg by 13%).

Cardiac arrhythmias, predominantly premature ventricular and supraventricular ectopic beats, as well as ventricular tachycardia, were observed sporadically. Arrhythmias were observed occasionally in the control period, with vehicle administration, with all of the drugs, in some of the animals, at each dose. There was no obvious pattern for the drugs, nor was a drug dose–response relation observed.

Pharmacokinetic Aspects

Blood drug concentrations were maximal at the end of the 3-min infusion period and decreased rapidly thereafter (fig. 5). As expected, drug concentrations in coronary sinus blood were at least 10 times those in arterial blood (fig. 6). The arterial drug concentrations, without exception, were far smaller than those associated with anesthesia. Over the time course sampled, there were no significant differences in the blood concentrations of *R*-

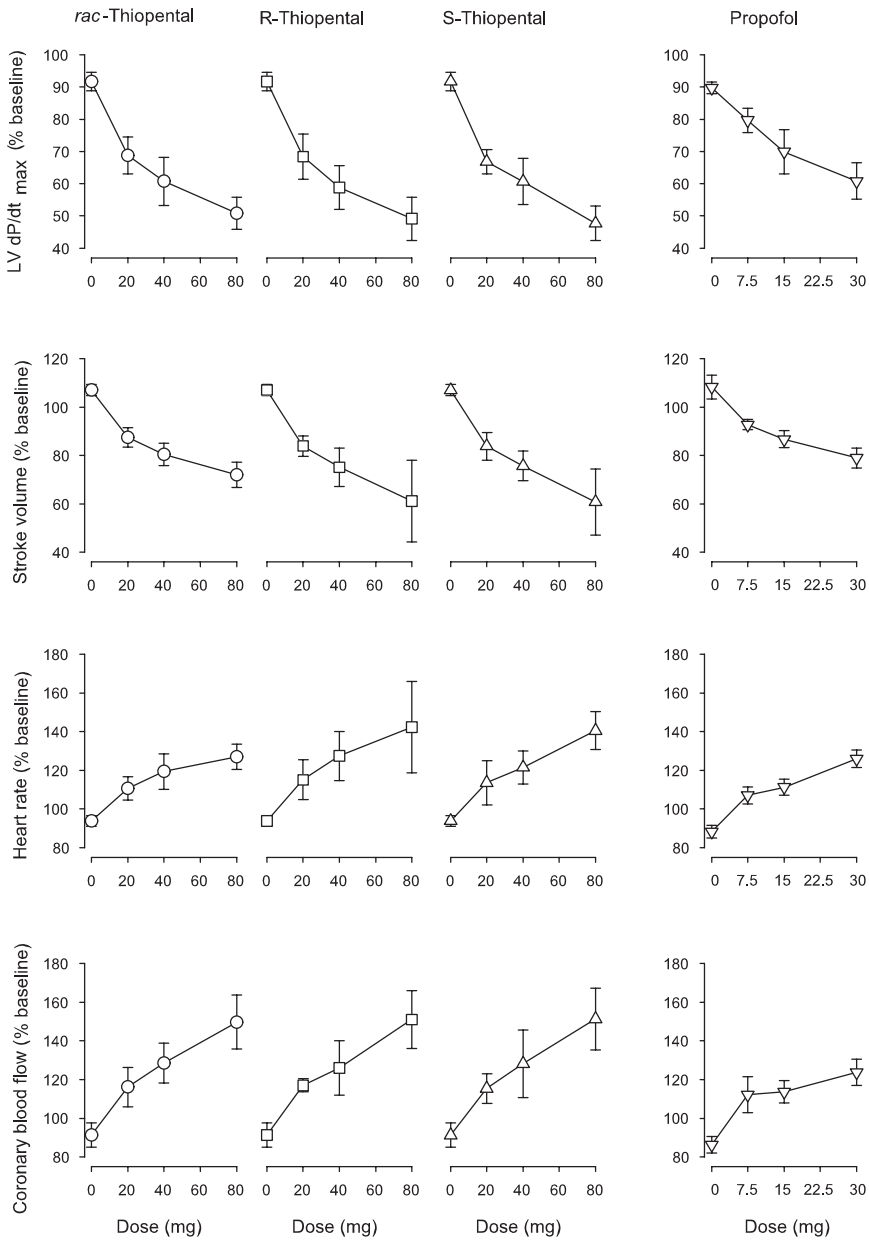

Fig. 3. Dose–effect relations for maximal changes in left ventricular dP/dt_{max}, stroke volume, left coronary artery blood flow, and heart rate from site-directed left main coronary arterial infusions of *rac*-, *R*-, and *S*-thiopental and propofol to conscious adult sheep. Mean values along with their 95% confidence intervals are shown.

and *S*-thiopental administered separately or as the components of *rac*-thiopental when scaled to dose.

Discussion

It is commonly taught that intravenous administration of thiopental for clinical anesthesia causes reductions in mean arterial blood pressure and cardiac output, along with tachycardia; that these effects result from a combination of direct reduction in myocardial contractility, directly induced venodilatation, and indirectly influence hemodynamics through depression of central control mechanisms[11]; and that propofol also causes these changes, but usually without an increased heart rate.[12] However, there is considerable debate about the root cause of the cardiovascular depression from these drugs, especially whether it is primarily a direct effect or mediated by effects on the CNS or peripheral vasculature.

Some of the uncertainty over direct *versus* indirect effects arises from inconsistent results found in different *in vivo* and *ex vivo* models used in its investigation. Apart from dose and dose rate, which have clear pharmacokinetic–pharmacodynamic implications,[13,14] a particular point that we believe leads to discrepancies among *in vivo* study results is whether and how the subjects are already anesthetized when studied, and whether they have been acutely or chronically prepared surgically for being studied. Anesthesia *per se* produces a panoply of hemodynamic and pharmacokinetic changes that differ somewhat according to anesthetic agent choice/conditions[15]—so, too, with the acute stress responses to surgery.[16] Under such circumstances,

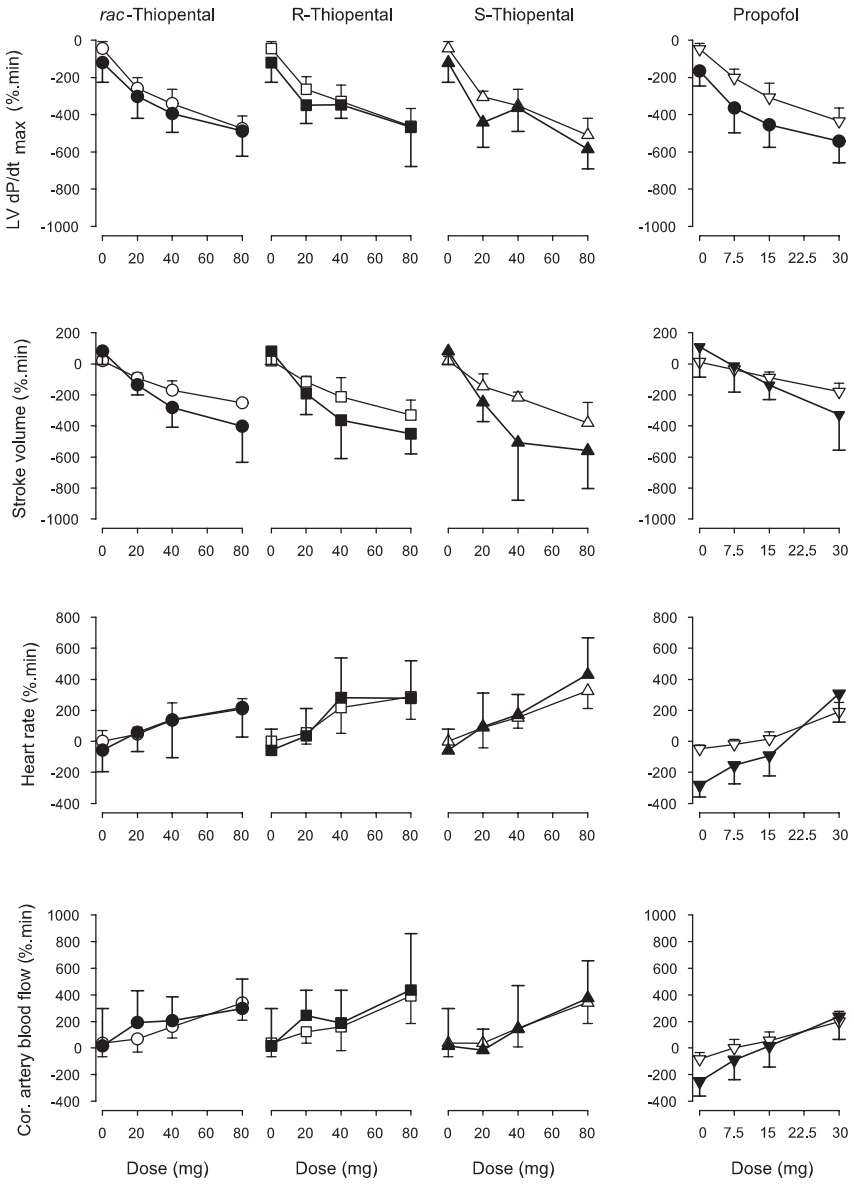

Fig. 4. Dose–effect relations for time integral of changes in left ventricular dP/dt_{max}, stroke volume, left coronary artery blood flow, and heart rate from site-directed left main coronary arterial infusions of *rac*-, *R*-, and *S*-thiopental and propofol to conscious adult sheep. Mean values for SED_5 (*open symbols*) and SED_{15} (*closed symbols*) along with their 95% confidence intervals are shown. SED = sum of effect differences.

it is arguable whether an observed cardiac drug response is true or damped, and even whether effects of test drugs can be satisfactorily differentiated from those of the background. Performing studies in a conscious chronic preparation can avoid this uncertainty when it is appropriate to do so.

This study was designed to avoid the background problem of anesthesia and surgery and to compare dose–response relations for the direct cardiac effects of thiopental enantiomers and propofol. The results provide unequivocal evidence of direct cardiac depression and of qualitatively and quantitatively similar effects of thiopental and propofol, with no material advantage of enantiopure thiopental over *rac*-thiopental.

To avoid complications caused by the indirect effects of the anesthetic agents on the CNS and peripheral vasculature in an *in vivo* preparation and of background general anesthesia, we used conscious subjects and a previously developed technique of site-directed left coronary arterial infusions with doses of test drugs believed to be insufficient to cause such extraneous effects. Our drug delivery approach had been validated previously both anatomically by vascular erosion casting and pharmacokinetically by measuring the resultant regional and systemic blood and heart tissue drug concentrations.[8] Such validation is necessary because of the potential for drug streaming in the affluent blood, thereby delivering an unforeseen pattern of tissue drug deposition. This can be precluded by placing the catheter tip at an appropriate predetermined site, in this case at the bifurcation of the left anterior descending and circumflex arteries, and using retrograde infusion to maximize turbulence. An abbreviated pharmacokinetic validation was repeated in the current studies by demonstrating that the recirculating drug concentrations in aortic blood were at least 10-fold less than those in coronary sinus blood (fig. 6)

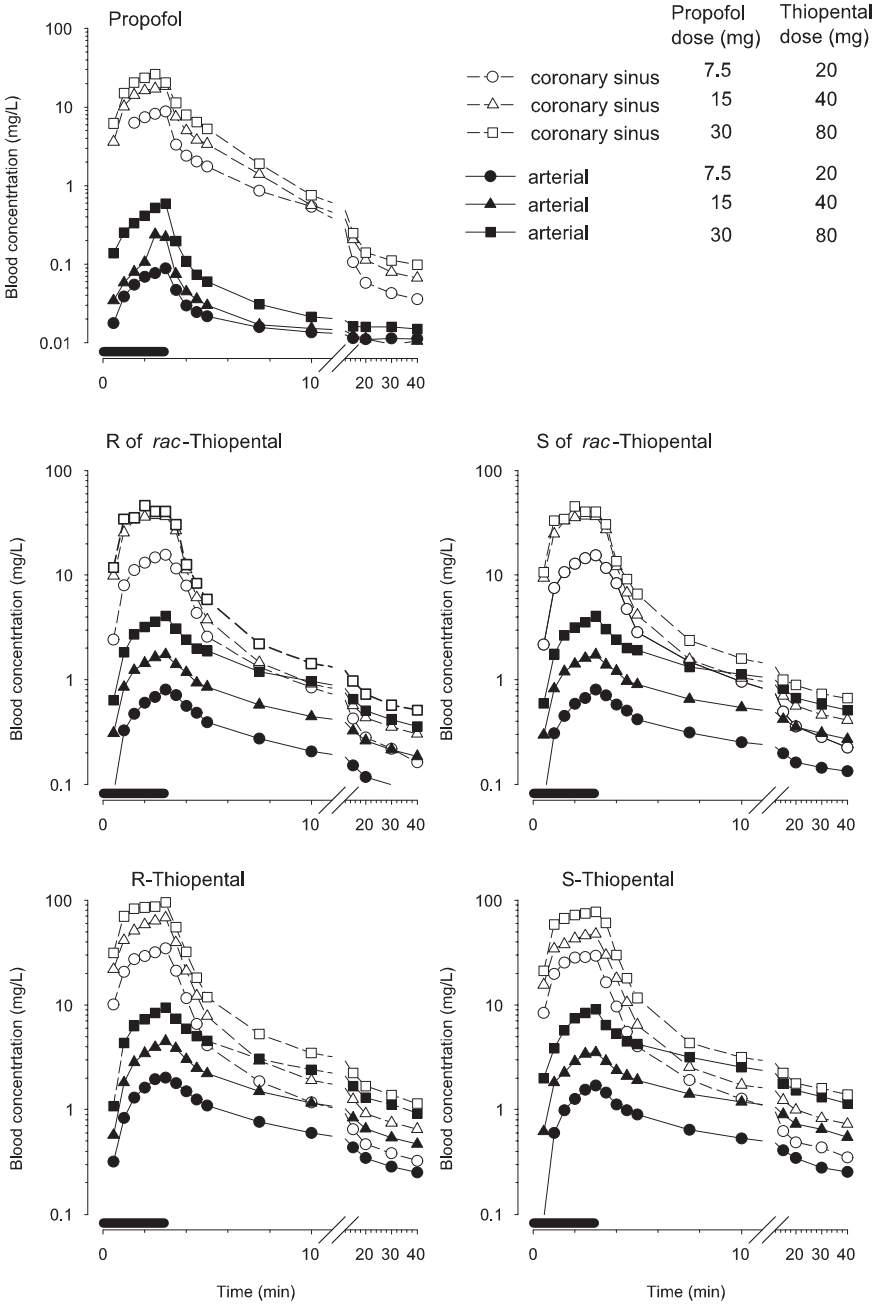

Fig. 5. Mean blood concentrations of thiopental enantiomers and propofol from site-directed left main coronary arterial infusions of *rac*-, *R*-, and *S*-thiopental. Individual enantiomer concentrations were determined by chiral separation after administration of *rac*-thiopental. The *horizontal bar* on the time axis indicates the period of drug infusion. Error bars for change have not been shown for clarity of display. Note time scale expansion.

and were much smaller than those usually associated with anesthesia.[11,12,17]

Several previous investigations have used intracoronary administration of thiopental, propofol, or both in large animals. One of these reported on cardiac function in previously prepared conscious dogs, but the purpose was to study ischemia–reperfusion injury, and the results were not directly applicable to the current objectives.[18] The others involved the use of anesthetized, usually paralyzed and ventilated, acutely prepared dogs[19–21] or sheep.[22] Although pharmacokinetic principles were recognized in the dosage regimens by estimating the drug concentrations delivered to the heart using dilution principles, only the most recent of these investigations actually measured the propofol concentrations in coronary sinus blood as a measure of myocardial drug exposure.[22]

Cardiovascular effects of *rac*-thiopental, sometimes in comparison to propofol, have been previously documented in a variety of rigorous experiments performed with *in vivo*[23–26] and *ex vivo* drug administration.[27–29] However, apart from differences in distribution to the heart relative to the CNS,[3] very little is known regarding the cardiovascular pharmacology of the thiopental enantiomers. A previous study performed in the isolated perfused rat heart with protein-free perfusate found no difference in the wash-in and wash-out kinetics of the thiopental enantiomers when administered as *rac*-thiopental.[30] The current study found that the *in vivo* car-

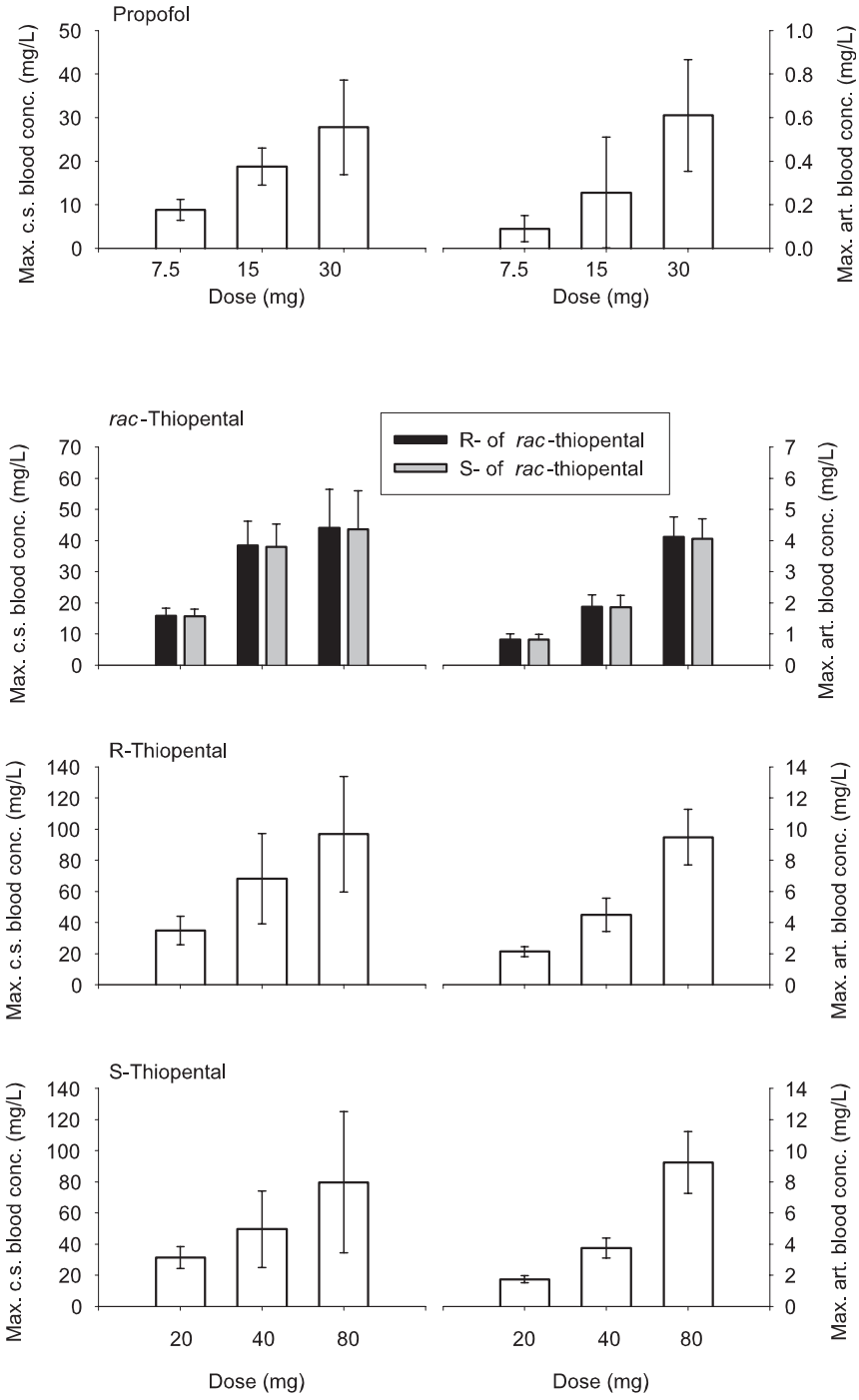

Fig. 6. Mean maximum measured coronary sinus (c.s.) and arterial (art.) blood concentrations of thiopental enantiomers and propofol from site-directed left main coronary arterial infusions over 3 min of *rac*-, *R*-, and *S*-thiopental and propofol to conscious adult sheep. Individual enantiomer concentrations were determined by chiral separation after administration of *rac*-thiopental. Mean values along with their 95% confidence intervals are shown.

diovascular effects of *rac*- and separately administered *R*- and *S*-thiopental were remarkably similar, but with a tendency of faster wash-in/wash-out of *R*-thiopental. Moreover, when scaled by dose to equianesthetic potency (in the sheep), the effects were also similar to propofol, which, although generally less in maximum effect, was usually more prolonged in duration.

Inotropic effect or change in inotropic state or both have been used in many studies as a basis for interpreting pharmacokinetic–pharmacodynamic models of anesthetic agents. In studies comparing the myocardial depression of thiopental and propofol *ex vivo*, thiopental has been found to cause greater depression than propofol, even when their relative anesthetic potencies were taken into account.[28,29] Various *in vivo* studies have reported dose-dependent negative inotropic effects of intravenous thiopental[24,25] and propofol.[31,32] A recent study found that the magnitude of the negative inotropic effect of propofol was strongly correlated with the measured propofol concentration in coronary sinus blood.[22] Taken together, these studies support the existence of a direct myocardial depressant effect of these drugs. In the

current study, the maximal negative inotropic effect of thiopental was extremely rapid in onset, again consistent with a primary direct effect, and with the high perfusion of the heart and facile drug diffusion from blood to effect sites. A previous study of *rac*-thiopental administered by intravenous infusion in sheep reported a small apparent volume of distribution in the heart and a calculated effect site equilibration half-time of 0.72 min.[24] In the current study, the time to maximal negative inotropic effect of propofol was only slightly longer than that of thiopental, but the rate of regression of its effect was much slower than that of thiopental, suggesting that its relative distribution into heart tissue is greater than thiopental. These differences are consistent with a calculated sheep heart tissue:plasma distribution coefficient of 0.36 for thiopental[24] and a calculated tissue:blood distribution coefficient of 5.94 for propofol.[33] However, these experiments have not determined the extent to which the regression of effect is prolonged by the triglyceride vehicle that accompanies propofol acting as a local drug depot.

The depressant effect of thiopental on stroke volume is consistent with a previous study in the dog that found direct effects on systolic shortening function by thiopental,[20] although in that study, propofol had no effect on systolic shortening and, in another study, only suprathrapeutic concentrations of propofol caused decreases in segmental shortening.[21] However, in our study, the time course of onset and regression of decrease in stroke volume was much slower than that of dP/dt_{max}, bearing a reciprocal relation with increases in heart rate; cardiac output, mean arterial blood pressure, and central venous pressure remained essentially unchanged. Other studies in the closed-chested dog have reported that intravenous propofol infusion decreased myocardial contractility and stroke volume,[31] but stroke volume was unaltered in open-chested subjects.[32] The subjects of the current study were closed chested. This is clearly another variable in experimental design and may help to explain why differences in results occur between different studies. Although species differences in sensitivity are recognized in principle, no systematic attempt has been made to examine *in vivo* cardiac effects of the intravenous anesthetics in different species with consistent methodology, as has been recently reported for propofol in an *ex vivo* model.[34] It is clear that different investigators develop particular expertise in specialized models, each claiming particular insights accordingly. However, for there to be more concerted gains, such as in evaluation of principles or new drugs, it seems that developing unifying principles in experimental design for particular aims deserves some urgent attention.

Although differences in the potency of the thiopental enantiomers have been known for some time,[35,36] potential clinical advantages of the less potent *R*-thiopental have been recognized only relatively recently. The principal advantages are because of its greater therapeutic index,[3] more favorable enantioselectivity of distribution between the heart and CNS,[3] and to its somewhat greater total body clearance,[5–7,37] although the latter may be mainly because of its higher plasma unbound fraction.[6,7,38] Even though such evidence has suggested that *R*-thiopental could make a suitable single enantiomer substitute for *rac*-thiopental, the current study did not find a significant difference in cardiac effects between enantiomers, although the rate of onset and regression of cardiac effects was consistent with a faster wash-in and wash-out of *R*-thiopental into cardiac tissues.

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References

1. Tucker GT: Chiral switches. Lancet 2000; 355:1085–7
2. Mather LE, Edwards SR, Duke CC: Electroencephalographic effects of thiopentone and its enantiomers in the rat. Life Sci 2000; 66:105–14
3. Mather LE, Edwards SR, Duke CC: Electroencephalographic effects of thiopentone and its enantiomers in the rat: Correlation with drug tissue distribution. Br J Pharmacol 1999; 128:83–91
4. Cordato DJ, Chebib M, Mather LE, Herkes GK, Johnston GA: Stereoselective interaction of thiopentone enantiomers with the $GABA_A$ receptor. Br J Pharmacol 1999; 128:77–82
5. Mather LE, Upton RN, Huang JL, Ludbrook GL, Gray E, Grant C: The systemic and cerebral kinetics of thiopental in sheep: Enantiomeric analysis. J Pharmacol Exp Ther 1996; 279:291–7
6. Cordato DJ, Gross AS, Herkes GK, Mather LE: Pharmacokinetics of thiopentone enantiomers following intravenous injection or prolonged infusion of racthiopentone. Br J Clin Pharmacol 1997; 43:355–62
7. Cordato, DJ Mather LE, Gross AS, Herkes GK: Pharmacokinetics of thiopental enantiomers during and following prolonged high-dose therapy. ANESTHESIOLOGY 1999; 91:1693–702
8. Chang DH-T, Ladd LA, Copeland S, Iglesias MA, Plummer JL, Mather LE: Direct cardiac effects of intracoronary bupivacaine, levobupivacaine and ropivacaine in the sheep. Br J Pharmacol 2001; 132:649–58
9. Huang JL, Mather LE, Duke CC: High-performance liquid chromatographic determination of thiopentone enantiomers in sheep plasma. J Chromatogr B 1995; 673:245–50
10. Mather LE, Selby DG, Runciman WB, McLean CF: Propofol: assay and regional mass balance in the sheep. Xenobiotica 1989; 11:1337–47
11. Fragen RJ, Avram MJ: Barbiturates, Anesthesia, 5th edition. Edited by Miller RD. Philadelphia, Churchill Livingstone, 2000, pp 209–27
12. Reves JG, Glass PSA, Lubarsky DA: Nonbarbiturate intravenous anesthetics, Anesthesia, 5th edition. Edited by Miller RD. Philadelphia, Churchill Livingstone, 2000, pp 228–72
13. Ludbrook GL, Upton RN, Grant C, Martinez A: The effect of rate of administration on brain concentrations of propofol in sheep. Anesth Analg 1998; 86:1301–6
14. Zheng D, Upton RN, Martinez AM, Grant C, Ludbrook GL: The influence of the bolus injection rate of propofol on its cardiovascular effects and peak blood concentrations in sheep. Anesth Analg 1998; 86:1109–15
15. Runciman WB, Myburgh J, Upton RN, Mather LE: Effects of anaesthesia on drug disposition, Mechanisms of Action of Drugs in Anaesthetic Practice, 2nd edition. Edited by Feldman SA, Scurr CF, Paton W. London, Edward Arnold, 1993, pp 83–128
16. Kehlet H: Modifications of responses to surgery by neural blockade: Clinical implications, Neural Blockade in Clinical Anesthesia and Pain Management, 3rd edition. Edited by Cousins MJ, Bridenbaugh PO. Philadelphia, Lippincott–Raven, 1998, pp 129–75
17. Russo H, Bressolle F: Pharmacodynamics and pharmacokinetics of thiopental. Clin Pharmacokinet 1998; 35:95–134
18. Yoo KY, Yang SY, Lee J, Im WM, Jeong CY, Chung SS, Kwak SH: Intracoronary propofol attenuates myocardial but not coronary endothelial dysfunction after brief ischaemia and reperfusion in dogs. Br J Anaesth 1999; 82:90–6
19. Chamberlain JH, Seed RG, Chung DC: Effect of thiopentone on myocardial function. Br J Anaesth 1977; 49:865–70

20. Belo SE, Kolesar R, Mazer CD: Intracoronary propofol does not decrease myocardial contractile function in the dog. Can J Anaesth 1994; 41:43–9

21. Ismail EF, Kim SJ, Salem MR, Crystal GJ: Direct effects of propofol on myocardial contractility in *in situ* canine hearts. ANESTHESIOLOGY 1992; 77:964–72

22. Zheng D, Upton RN, Martinez AM: The contribution of the coronary concentrations of propofol to its cardiovascular effects in anesthetized sheep. Anesth Analg 2003; 96:1589–97

23. Runciman WB, Mather LE, Selby DG: Cardiovascular effects of propofol and of thiopentone anaesthesia in the sheep. Br J Anaesth 1990; 65:353–9

24. Upton RN, Huang YF, Grant C, Gray EC, Ludbrook GL: Myocardial pharmacokinetics of thiopental in sheep after short-term administration: Relationship to thiopental-induced reductions in myocardial contractility. J Pharm Sci 1996; 85:863–7

25. Huang YF, Upton RN, Gray EC, Grant C, Zheng D, Ludbrook GL: The effects of short intravenous infusions of thiopentone on myocardial function, blood flow and oxygen consumption in sheep. Anaesth Intensive Care 1997; 25:627–33

26. Upton RN, Ludbrook GL: A model of the kinetics and dynamics of induction of anaesthesia in sheep: Variable estimation for thiopental and comparison with propofol. Br J Anaesth 1999; 82:890–9

27. Park WK, Lynch C III: Propofol and thiopental depression of myocardial contractility: A comparative study of mechanical and electrophysiological effects in isolated guinea pig ventricular muscle. Anesth Analg 1992; 74:395–405

28. Azari DM, Cork RC: Comparative myocardial depressive effects of propofol and thiopental. Anesth Analg 1993; 77:324–9

29. Süzer Ö, Süzer A, Aykaç Z, Özüner Z: Direct cardiac effects in isolated perfused rat hearts measured at increasing concentrations of morphine, alfentanil, fentanyl, ketamine, etomidate, thiopentone, midazolam and propofol. Eur J Anaesthesiol 1998; 15:480–5

30. Nguyen KT, Morgan DJ: Myocardial uptake of thiopental enantiomers by the isolated perfused rat heart. Chirality 1996; 8:477–80

31. Pagel PS, Warltier DC: Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. ANESTHESIOLOGY 1993; 78:100–8

32. Hettrick DA, Pagel PS, Warltier DC: Alterations in canine left ventricular-arterial coupling and mechanical efficiency produced by propofol. ANESTHESIOLOGY 1997; 86:1088–93

33. Weaver BM, Staddon GE, Mapleson WW: Tissue/blood and tissue/water partition coefficients for propofol in sheep. Br J Anaesth 2001; 86:693–703

34. van Klarenbosch J, Stienen GJ, de Ruijter W, Scheffer GJ, de Lange JJ: The differential effect of propofol on contractility of isolated myocardial trabeculae of rat and guinea-pig. Br J Pharmacol 2001; 132:742–8

35. Christensen HD, Lee IS: Anesthetic potency and acute toxicity of optically active disubstituted barbituric acids. Toxicol Appl Pharmacol 1973; 26:495–503

36. Haley TJ, Gidley JT: Pharmacological comparison of R(+), S(-) and racemic thiopentone in mice. Eur J Pharmacol 1976; 36:211–4

37. Mather LE, Edwards SR, Duke CC, Cousins MJ: Enantioselectivity of thiopental distribution in the central neural tissue of rats: An interaction with halothane. Anesth Analg 1999; 89:230–5

38. Nguyen KT, Stephens DP, McLeish MJ, Crankshaw DP, Morgan DJ: Pharmacokinetics of thiopental and pentobarbital enantiomers after intravenous administration of racemic thiopental. Anesth Analg 1996; 83:552–8