EFFECTS OF PROPOFOL AND OF THIOPENTONE
ANAESTHESIA ON THE RENAL CLEARANCE OF
CEFOXITIN IN THE SHEEP

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SUMMARY

We have examined the renal extraction ratios and clearances of cefoxitin in three groups of adult merino ewes. One group (n = 3) was studied for 12 h without perturbation; these were designated control studies. The other two groups (n = 4 each) were studied before (baseline values), during and after the induction and 70-min maintenance of anaesthesia with propofol or thiopentone. In the control studies, mean renal extraction ratio and clearance for cefoxitin were, respectively, 0.67–0.92 and 0.66–0.91 litre min⁻¹ and were consistent throughout the entire study period in individual animals. Comparable values were obtained as baseline values in the anaesthesia groups. Compared with individual baseline values, blood concentrations of cefoxitin doubled during anaesthesia with each agent. At the same time, renal extraction ratio and clearance for cefoxitin each decreased significantly to about 50–60% of their control values. Recovery to control values of arterial blood concentrations and renal extraction ratio of cefoxitin took at least 5 h, but recovery of renal clearance was more rapid. The results indicate that renal elimination of an organic anion such as cefoxitin may be affected by changes in renal blood flow and in renal function produced by propofol and thiopentone; these effects may last for several hours after recovery of renal blood flow.

KEY WORDS


It has been observed that the response of the kidney to anaesthesia and surgery is complex [1, 2]. The effects of anaesthesia, alone, on the renal clearance of drugs and other substances are thus difficult to determine and are in need of clarification. With the current interest in the use of propofol and the resurgence of interest in thiopentone for “infusion” anaesthesia, it was decided to study the effects of total anaesthesia with these agents on the renal elimination of cefoxitin, an antibiotic substance which is essentially eliminated totally from the body by glomerular filtration and renal tubular secretion [3], in sheep prepared in such a way as to allow simultaneous cardiovascular and regional pharmacokinetic measurements.

METHODS

The studies were performed in three groups of sheep prepared previously with chronically implanted intravascular cannulae so that the renal blood flow and renal extraction of cefoxitin could be measured. In the first group, studies were performed in the absence of any perturbations: these were designated control studies. The other two groups were studied before (baseline measurements), during (anaesthesia measurements) and after (recovery measurements) total i.v. anaesthesia with propofol or thiopentone. The details of the preparation of the animals, the methods and the cardiovascular effects of propofol and of thiopentone anaesthesia are reported.
RENAL EFFECTS OF PROPOFOL AND THIOPENTONE

Adult merino ewes (weight 33–51 kg) were prepared with polyethylene catheters with their tips in the ascending aorta, in the right atrium and in the left renal vein. On the day of each study, right atrial infusions of cefoxitin and hippuran were made for 12 h for measurement of renal blood flow. In the anaesthesia studies, the first 60-min period was designated for loading infusions and to allow the animal to adapt to the study room. During the next 30-min period, observations were made and appropriate blood samples were collected 10 min apart (i.e. four sets) for baseline measurements. Anaesthesia was induced with either propofol 250–300 mg over 1 min (n = 4) or thiopentone 750 mg over 1 min (n = 4), a cuffed tracheal tube was inserted and the lungs were ventilated to normocapnia with an \(F_{\text{io}}\) of 0.4. Maintenance infusions of propofol 20–25 mg min\(^{-1}\) at a constant rate or thiopentone 25 mg min\(^{-1}\) reducing to 10 mg min\(^{-1}\) over 30 min were continued for 70 min. The last 30 min of this period was observed as the “anaesthesia period” and measurements were made as for the control period. After the maintenance infusions were stopped, recovery was observed by repeating the measurements at 0.5, 1.0, 2, 3, 4, 5, 6, 7, 8 and 9 h. For subsequent statistical analysis, these were grouped into early (0.5–2 h), mid (3–5 h) and late (6–9 h) recovery periods. Arterial blood concentrations of propofol and thiopentone were measured by high pressure liquid chromatography (HPLC) [5, 6] to correlate the dissipation of renal effects with the distribution and metabolism of the anaesthetic agents.

Cefoxitin sodium was infused using a two-stage regimen to produce constant arterial blood concentrations [3]. Loading doses (22.6 mg min\(^{-1}\) for 15 min) were followed immediately by maintenance infusions (11.5 mg min\(^{-1}\)) for 12 h. Arterial and renal venous blood concentrations of cefoxitin were determined by HPLC [3]. The renal clearances of cefoxitin were determined from the products of the renal blood flow and respective renal extraction ratios.

A longitudinal study design was used in the anaesthesia groups that permitted detection of significance with small sample sizes. The respective mean value in the control periods of each individual study was assigned a value of 100% and one-sample \(t\) tests against this value were performed on the means and sd for each parameter.

**FIG. 1.** Individual arterial blood concentrations of cefoxitin in three sheep in the control studies, and four in the propofol and four in the thiopentone anaesthesia studies. After a loading infusion of 22.6 mg min\(^{-1}\) for 15 min, cefoxitin was administered by constant rate infusion at 11.5 mg min\(^{-1}\) throughout the studies. In the control studies, the respective mean arterial blood concentrations of cefoxitin in the three animals were 13.7 (SD 2.1), 7.0 (0.6) and 13.3 (0.9) mg litre\(^{-1}\); the respective renal venous concentrations were 4.2 (0.7), 2.2 (0.8) and 1.1 (0.4) mg litre\(^{-1}\); respective renal extraction ratios of cefoxitin were 0.69 (0.03), 0.67 (0.14) and 0.92 (0.03) and the corresponding renal clearances of cefoxitin 0.66 (0.09), 0.91 (0.20) and 0.89 (0.16) litre min\(^{-1}\). For the anaesthesia studies, the period of anaesthesia is indicated by the broken vertical lines.
The effects of propofol (open panels) and thiopentone (hatched panels) anaesthesia on renal extraction ratio and renal clearance of cefoxitin during constant rate infusion in the sheep. To facilitate comparisons between time periods, the individual mean values during the 30-min period immediately before anaesthesia have been assigned a value of 100% (baseline) and values during subsequent periods have been expressed as percentage mean and SD of this value. Test periods were observed during the last 30 min of a 70-min period of anaesthesia (GA), during early recovery (0.5-2 h), during mid recovery (3-5 h) and during late recovery (6-9 h).

Statistical significance (two-tailed): *P < 0.05; **P < 0.01.

RESULTS

Similar values were observed in the control studies and in the baseline periods of the anaesthesia studies. In the control studies, there were no significant cardiovascular changes caused by administration of cefoxitin and the blood concentrations of cefoxitin remained essentially constant throughout the entire study period (fig. 1). In marked contrast to the constancy of the control and baseline observations, anaesthesia with each anaesthetic agent caused the cefoxitin blood concentrations to increase abruptly, although a new steady state could not be determined in every case within the anaesthesia period (fig. 1). The overall mean arterial blood concentrations of the anaesthetic agents during this period were propofol 8.4 (sd 2.2) mg litre⁻¹ and thiopentone 47 (21) mg litre⁻¹.

The mean cefoxitin renal extraction ratios during propofol and thiopentone anaesthesia were, respectively, 70 (12)% (P < 0.05) and 66 (10)% (P < 0.01) of their respective baseline values (fig. 2); the corresponding mean renal clearances of cefoxitin were 60 (22)% (P < 0.05) and 49 (11)% (P < 0.01) of their respective baseline values (fig. 2). During this period, the mean renal blood flow was reduced during thiopeptone anaesthesia to a mean of 73 (9)% (P < 0.05) of baseline, but it was not changed significantly during propofol anaesthesia (mean 80 (20)%, of baseline values). Although mean arterial blood concentrations of propofol were less than 0.1 mg litre⁻¹ by 2-3 h after anaesthesia, recovery to baseline values of the mean renal extraction ratio of cefoxitin after propofol anaesthesia was not observed within the recovery period, although renal clearance of cefoxitin was not significantly different from baseline by the mid recovery period. The mean arterial blood concentration of thiopentone 4 h after anaesthesia was 8.9 (1.7) mg litre⁻¹ or 21 (7)% of the individual mean values during anaesthesia. Recovery to baseline values of the mean renal extraction ratio of cefoxitin after thiopentone anaesthesia had occurred by the late recovery period and, although renal clearance of cefoxitin was not significantly different from baseline by the mid recovery period, it was again less than baseline in the late recovery period.

DISCUSSION

In the control studies and during the baseline period of the anaesthesia studies, the blood concentrations of cefoxitin remained essentially constant. During anaesthesia with propofol or with thiopentone, mean arterial blood concentrations of cefoxitin were approximately twice those immediately preceding anaesthesia. This could have been caused by decreased rate of elimination, a decreased extent of tissue distribution or both. The study design used was not able to determine the effects of anaesthesia on distribution, but it was observed that both...
anaesthetic agents markedly decreased the renal extraction ratio and clearance of cefoxitin. Only thiopentone decreased the renal blood flow significantly [4]. Although a new steady state was not necessarily achieved in each animal within the anaesthesia period, the resultant errors for drug equilibration within the highly perfused kidneys was believed to be acceptably small.

Cefoxitin is excreted renally by both glomerular filtration and tubular secretion. It is known that its rate of elimination is decreased in the presence of renal dysfunction [7]. Similar effects were caused by anaesthesia. Although it is possible that the renal effects of anaesthesia were mediated, at least in part, through competition for secretion between renally excreted metabolites of the anaesthetics and cefoxitin—as has been reported, for example, to occur in the presence of probenecid [8, 9]—it is probable that propofol and thiopentone share the depressant effects of the volatile anaesthetic agents on renal function [10, 11] which have also been observed for thiopentone in kidney slices in vitro [12]. Such effects on renal blood flow and renal function, it would seem, are common among general anaesthetic agents [10–17]; the differences between agents would seem to be mainly those of magnitude and time course. Although the clearance of propofol from the blood was much faster than that of thiopentone and the animals apparently recovered faster as judged by earlier extubation and standing, the effects of propofol on elimination of cefoxitin were not of a clearly shorter duration than thiopentone. This, too, suggests that the time course of effects of the anaesthetics may have been regulated by recovery of the same metabolically active process in the renal tubules.

The widespread use of propofol has prompted the need for further studies of its full range of pharmacological properties, including its effects on regional blood flow and on the kinetics of biologically relevant substances. Although the renal effects of these agents do not appear to be as great as those of the volatile anaesthetic agents, they are nevertheless appreciable, so that the kinetics of pharmacotherapeutic agents may be altered for many hours after apparent recovery from anaesthesia. Analogous studies of the effects of propofol and thiopentone on the regional pharmacokinetics of pethidine have been reported separately [18].

ACKNOWLEDGEMENTS

The authors acknowledge the support of the National Health and Medical Research Council of Australia, the Faculty of Anaesthetists of the Royal Australasian College of Surgeons and the technical assistance of Mrs R. Carapetis, Ms E. Hennig, Ms J. Tubb, Ms G. Summersides, Mr C. McLean and Mr K. Smart.

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