CARDIOVASCULAR EFFECTS OF A CHLORMETHIAZOLE INFUSION IN COMBINATION WITH EXTRADURAL ANAESTHESIA

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Although the use of chlormethiazole (CTZ) was considered inappropriate for the induction and maintenance of anaesthesia (Dundee, 1958) on account of the lack of analgesic activity, more recent reports (Schweitzer, 1978; Mather and Cousins, 1980) have suggested that it is a useful agent with which to provide sedation during surgery performed under regional anaesthesia. Previous studies of the cardiovascular effects of CTZ, both as sole agent in healthy volunteers (Wilson, Stephen and Scott, 1969) and in combination with nitrous oxide and pethidine in general anaesthesia (Christensen, Andreasen and Kristoffersen, 1983) have shown acceptable cardiovascular stability. However, while drugs producing marked sedation may have few adverse cardiovascular effects when given alone, this may not be so when they are combined with extradural anaesthesia, since the latter causes widespread sympathetic blockade. The present study was undertaken to assess the cardiovascular effects of CTZ when administered in association with extradural blockade.

PATIENTS AND METHODS

Six female patients scheduled for major gynaecological surgery, for which extradural anaesthesia was considered appropriate, agreed to take part in this study. No patient had a history of cardiac disease nor was any taking medication likely to affect the cardiovascular system. The nature of the study, which had approval from the local ethics committee, was explained and the patient's consent obtained.

One hour before the start of the study, five patients received diamorphine 5 mg and atropine 0.6 mg, and one patient (aged 67 yr) received diamorphine 2.5 mg and atropine 0.6 mg i.m. An extradural catheter was inserted at the L3-4 intervertebral space. Cardiovascular variables were monitored non-invasively using a Minnesota Impedance Cardiograph (Model 304 A) coupled with a Bell and Howell oscillograph (Model 5-137) and Dynamap 840 arterial pressure monitor. Mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), stroke volume (SV), left ventricular ejection time (LVET) and pre-ejection period (PEP) were calculated. The resistivity of blood was calculated from the patient's haematocrit using the formula $\rho = 2.102 \times Hct + 30.098$ (Hill and Thomson, 1975).

With the patient lying supine and comfortable, three sets of recordings were obtained at intervals of 2 min to obtain control data. Sixteen to eighteen millilitre of 2% lignocaine was injected via the extradural catheter and further sets of recordings obtained at 2, 4, 6 and 8 min following injection. At this point, a rapid infusion of 0.8% CTZ (30-40 ml min$^{-1}$ i.v.) was given until the patient became unconscious. The infusion rate was then adjusted to

SUMMARY

The cardiovascular effects of an infusion of chlormethiazole 30–40 ml min$^{-1}$ were studied in six patients following an extradural injection of 2% lignocaine. There were small but statistically significant decreases in mean arterial pressure and left ventricular ejection time during the infusion. Increases in the pre-ejection period were noted, but there were no significant changes in cardiac output, stroke volume or heart rate. Patient acceptance was high. It is concluded that sedation with an infusion of chlormethiazole, during surgery carried out under extradural anaesthesia, has no clinically adverse cardiovascular effects.
maintain sedation of such a degree that the patients were either quite unresponsive or virtually so. Four further sets of measurements were obtained at 2, 4, 6 and 8 min from the start of the chlormethiazole infusion. Following the final series of measurements, patients were prepared for surgery, and the chlormethiazole infusion continued to provide adequate sedation during the operation.

Statistical analysis of the data was performed using Wilcoxon’s matched pair signed rank test, \( P < 0.05 \) being taken to indicate statistical significance.

**RESULTS**

All patients underwent major vaginal surgery and the combination of extradural analgesia and sedation with CTZ proved satisfactory in all. The ages of the patients ranged from 33 to 67 yr (mean 51 yr), their weights from 54.0 to 89.9 kg (mean 65.6 kg) and their heights from 152.4 to 165.1 cm (mean 159.6 cm).

Deep sedation was produced following the rapid infusion of 0.8% CTZ approximately 70–100 ml and the mean total CTZ infused over the 8 min of the study was 190 ml (range 125–220 ml).

**Cardiovascular variables**

Mean data (± SEM) for each set of recordings are displayed in figure 1. Figure 2 shows the mean control values from each patient, the values 8 min following the extradural injection, and the lowest MAP, CO, SV, LVET and highest HR and PEP during the chlormethiazole infusion, these being considered the least desirable changes caused by CTZ.
after the start of the infusion when compared with control values. Similarly, there were small but statisti-
cally significant decreases in LVET 4 and 6 min following the start of the CTZ infusion but continued during the CTZ infusion. The lowest arterial pressure recorded during the study period was 89/53 mm Hg.

Stroke volume. There was a small but insignificant decrease in stroke volume which was associated with an increase in heart rate. This was noted initially during the period following the extradural injection and then remained fairly constant during the CTZ infusion. Two patients had tachycardia with heart rates of 142 and 128 beat min⁻¹ immediately following the start of the CTZ infusion but, during the second 4 min of the CTZ infusion, their heart rates decreased to values similar to those immediately preceding the infusion.

Systolic time indices. There were small but statistically significant decreases in LVET 4 and 6 min after the start of the CTZ infusion when compared with control values. Similarly, there were small but statistically significant increases in PEP 6 and 8 min after the start of the infusion when compared with control and pre-infusion data.

DISCUSSION

Before this study, it had been our clinical impression that the combination of extradural blockade and sedation with a CTZ infusion produced haemodynamically stable conditions. Schweitzer (1978), and Mather and Cousins (1980) have also commented on this, but no study of the detailed cardiovascular effects of the combination has been published. Although starting the infusion of CTZ before the extradural puncture has been suggested by Seow and colleagues (1981)—to make the procedure more comfortable for patients—it has been our practice to perform the extradural puncture first in the awake, co-operative patient. By doing so in this study, we were able to study the effects of CTZ in patients who had some degree of sympathetic blockade and were arguably more vulnerable to any adverse cardiovascular effect.

The initial rate of infusion (30-40 ml min⁻¹) was fast and rapidly produced loss of consciousness. In a previous study of the cardiovascular effects of CTZ in healthy volunteers Wilson, Stephen and Scott (1969) used 12–20 ml min⁻¹. However, the initial infusion rate used in this study is the more common in clinical use and would be expected to show any deleterious cardiovascular effects, if they existed.

Although there were statistically significant decreases in arterial pressure, the lowest value recorded was 89/53 mm Hg. No fluids were infused i.v. during the study period except 0.8% CTZ, and no patient required a vasopressor. A decrease in arterial pressure of this degree is common during extradural anaesthesia, and it is interesting to note that Seow and colleagues (1981) noticed an increase of 27% in systolic arterial pressure during the first few minutes of chlormethiazole infusion in healthy volunteers. Cardiac output and stroke volume were stable during the trial period. Two of our patients experienced transient increases in heart rate at the start of the infusion, but these settled within a few minutes. This contrasts with studies in healthy volunteers, in whom Wilson, Stephen and Scott (1969) noticed an average increase of 48.7% and Seow and co-workers (1981) recorded an increase of 50% over resting heart rate, and it was for this reason that CTZ infusion was suggested as a supplement to extradural anaesthesia. Certainly, none of our patients experienced a bradycardia: the slowest heart rate recorded was 83 beat min⁻¹. The small, but statistically significant, changes in systolic time indices had no noticeable effect on cardiac output. Christensen, Andreassen and Kristoffersen (1983) noticed similar changes in systolic time indices when CTZ was infused during general anaesthesia, but these changes were much smaller than during a thiopentone infusion.

Patient acceptance of this method of anaesthesia was high in this study.

Patients awoke rapidly when the infusion was stopped at the end of their operation. Seow, Mather and Roberts (1981), studying the pharmacokinetics and pharmacodynamics of CTZ, came to the conclusion that it was a good choice for i.v. sedation because of its rapid clearance and short elimination half-life. In that study, psychometric testing was carried out and showed a return to normal within 30 min of cessation of the infusion in heavily sedated patients.
volunteers. We believe that the properties of rapid awakening and cardiovascular stability support the use of an infusion of chlormethiazole to produce sedation during surgical procedures carried out under extradural blockade.

REFERENCES


