TWO-STAGE INFUSION OF CHLORMETHIAZOLE FOR BASAL SEDATION

L. T. SEOW, J. G. ROBERTS, L. E. MATHER AND M. J. COUSINS

SUMMARY
The effectiveness of chlormethiazole in providing basal sedation was studied using a two-stage infusion regimen consisting of an initial loading dose of 60 mg min^{-1} for 25 min (in the lateral position) followed by a maintenance constant-rate infusion of 10 mg min^{-1} for 60 min (in the supine position). The regimen was evaluated in five healthy young volunteers who were all moderately sedated throughout most of the infusion, lapsing into sleep when left undisturbed, yet awakened easily to obey commands. Varying periods of amnesia, corresponding with a mean chlormethiazole ethanedisulphonate blood concentration of 10.3 mg litre^{-1} (SD 3.8) were obtained. Light sedation occurred during the first 10 min and the last 20 min of the total infusion period, corresponding to chlormethiazole blood concentrations of 7.9 mg litre^{-1} (SD 1.9) and 7.4 mg litre^{-1} (SD 2.3) respectively. Adverse side-effects were transient nasal irritation, flushing and a coryza-like syndrome. Other side-effects of tachycardia and hypertension may be beneficial in counteracting cardiovascular depression associated with central neural blockade. A high total body clearance of chlormethiazole (mean 1.39 litre min^{-1}, SD 0.58) was found and would contribute to the brief duration of action after termination of the infusion.

An increasing number of radiological, endoscopic and major surgical procedures are performed under topical, local or regional analgesia and many of the patients require some form of sedation or narcosis. Narcosis induced by nitrous oxide has been used, but was limited by problems of insufficient depth of unconsciousness and unpleasant dreams. The use of a volatile agent such as halothane to produce narcosis may produce decreases in cardiac output, bradycardia or loss of airway support. Thus the development of an i.v. sedative technique, which produces minimal cardiorespiratory depression, maintains airway reflexes and provides amnesia would be a distinct advantage.

Precise control of the level of sedation during regional analgesia has posed a challenge to the anaesthetist. A variety of central nervous system (c.n.s.) depressant agents, administered in different doses and regimens, together with various psychological approaches to patients, has been used. Most of these suffer from complex dose regimens or prolonged drowsiness following surgery because of the use of long-acting drugs. Recent studies have suggested that chlormethiazole may be valuable in this context (Mather and Cousins, 1980; Seow, Mather and Roberts, 1981).

This study was designed to assess the efficacy of a two-stage infusion of chlormethiazole in maintaining a state of basal sedation similar to that required during operations performed under regional anaesthesia. This was tested in young healthy volunteer subjects, in the absence of surgical stress and concomitant drugs. During this study pharmacokinetic and pharmacodynamic characteristics of chlormethiazole were determined in relation to those postural changes often encountered during the performance of extradural or spinal blockade. Volunteer studies of this kind are a prerequisite to the design of safe clinical trials in patients and any differences occurring between the volunteers and patients help to elucidate the physiology of patients presenting for surgery.

SUBJECTS AND METHODS
Five healthy adult volunteers, aged 18–21 yr, and weighing 49–80 kg were studied (table I). Informed consent was obtained after a detailed explanation of the plan. Criteria for selection of the subjects, preparation for the study and the monitoring of the subjects, were as described previously (Mather et al., 1981; Seow, Mather and Roberts, 1981). After a rest period of 1 h following insertion of i.v. lines, the clearance of indocyanine


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TABLE I. Physical characteristics of volunteer subjects

<table>
<thead>
<tr>
<th>Subject number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
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<td>18</td>
<td>19</td>
<td>19</td>
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<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Weight (kg)</td>
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<td>69</td>
<td>69</td>
<td>80</td>
<td>50</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>Height (cm)</td>
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<td>180</td>
<td>161</td>
<td>192</td>
<td>151</td>
<td>172</td>
<td>15</td>
</tr>
</tbody>
</table>

green (Austin, Stapleton and Mather, 1981) was determined in all subjects in the supine position and, in four subjects, in the left lateral position 30 min later, to evaluate the postural effects which may alter liver blood flow and the blood concentrations of chlormethiazole.

Chlormethiazole ethanedisulphonate 0.8% (Heminevrin, CTZ) was administered by a two-stage infusion, designed to achieve a moderately sedated clinical state:

(a) A loading infusion of 60 mg min⁻¹ CTZ (7.5 ml min⁻¹) was administered at a constant rate for 25 min with the subject in the left lateral position, followed immediately by:

(b) A maintenance infusion of 10 mg min⁻¹ CTZ (1.25 ml min⁻¹) at a constant rate for 60 min, with the subject supine.

The CTZ solution was infused with a Braun “Infusomat” pump into a left antecubital vein. Throughout the infusion, arterial pressure, heart rate and respiratory rate were monitored at 5-min intervals whilst finger plethysmography, e.g., skin temperature and state of consciousness were monitored continuously. Higher mental faculties were assessed every 15 min by a psychometric test called Paced Auditory Serial Addition Tasks (PASAT) (Gronwall and Sampson, 1974; Mather et al., 1981).

Blood samples (1.0 ml) for CTZ analyses were taken from the contralateral axillary vein at the following times: before commencing infusion, every 5 min for 45 min (during the 25 min of loading infusion and for first 20 min of maintenance infusion), every 10 min until the end of the infusion, every 5 min for 20 min after cessation of infusion, every 10 min for the next 20 min and then at 20-min intervals for the next 4 h. Axillary vein blood rather than central venous blood was obtained to avoid sampling blood enriched with CTZ being infused in the contralateral antecubital vein. A non-linear least squares routine on a digital computer was used to derive empirical biexponential equations corrected for double infusions which described the relationship between blood concentrations and time (Mather, Ringrose and Austin, 1979). From the coefficients and exponents of these equations, the constants of a two-compartment open model were derived (Austin, Stapleton and Mather, 1981).

CTZ analyses were performed using a solvent extraction (Mather and Tucker, 1974) and gas chromatographic analysis technique similar to that recently reported by Tsuei, Thomas and Nation (1980) except that an OV 225 column was used. Accuracy and sensitivity were the same as those reported by Tsuei, Thomas and Nation and the OV 225 column also resolved CTZ and its internal standard bromethiazole (BTZ), from two of its prime metabolites, the ketone (5-acetyl-4-methylthiazole; AMT) and the secondary alcohol (5-((1-hydroxyethyl)-4-methylthiazole; HEMT), both formed by oxidation of the chloroethyl side chain (Moore, Robertson et al., 1975; Nation et al., 1977). An additional metabolite was noted in gas chromatograms but was not measured as no authentic reference substance was available. This metabolite was subjected to structural analysis using combined gas chromatography–mass spectrometry. For this analysis, the same gas chromatographic conditions were used to separate the compounds. The instrument used was a Hewlett–Parkard Model 5995 gas chromatograph–mass spectrometer operating with electron impact ionization at 70 eV.

RESULTS

The physical characteristics of the subjects are shown in table I. Each subject received CTZ 60 mg min⁻¹ for 25 min in the left lateral position (one subject (No. 3) received this regimen for 20 min only as she was deeply sedated at that time). The subsequent constant-rate infusion of 10 mg min⁻¹ was administered to all subjects in the supine position for 60 min.

A representative curve of blood CTZ concentrations (expressed as the salt in mg litre⁻¹) plotted against time, during and after infusion, is shown in figure 1. CTZ blood concentrations increased rapidly with the loading infusion. A very light level of sedation, associated with yawning, occurred in all subjects 7–10 min after commencing the infusion; the mean CTZ blood concentration was 7.9 mg litre⁻¹ (SD 1.9). The maximum CTZ blood concentrations were achieved in all
CHLORMETHIAZOLE INFUSION FOR SEDATION

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(a) 60 mg min⁻¹ CTZ infusion for 25 min

(b) 10 mg min⁻¹ CTZ infusion for 60 min

FIG. 1. Blood concentrations of chlormethiazole (mg litre⁻¹ salt) following a two-stage infusion regimen consisting of (a) 60 mg min⁻¹ (0.8% CTZ 7.5 ml min⁻¹) for 25 min; (b) 10 mg min⁻¹ (1.25 ml min⁻¹) for 60 min in one subject (No. 2). The continuous line depicts a computer-fitted curve describing two-compartment open model kinetics. I = Light sedation; II = moderate sedation with amnesia; III, IV = rapid decrease in blood CTZ concentrations reflecting rapid redistribution.

subjects at the end of the loading infusion and ranged from 11.3 mg litre⁻¹ (associated with a clinical state of moderate sedation) to 25.1 mg litre⁻¹ (deeply sedated), with a mean value of 18.5 mg litre⁻¹ (SD 5.0) (table II). However, with the commencement of the maintenance infusion the initially high CTZ blood concentrations were not sustained, but decreased rapidly to reach a plateau during the last 20 min of infusion. Thoughout most of the loading infusion (except for subject No. 3 who was deeply sedated for 2 min) all other subjects were moderately sedated. They lapsed into a sleep-like state when left undisturbed, but were easily aroused to obey commands; while awake, all would agree to do the psychometric test, PASAT, but would lapse into sleep almost immediately after starting the test. This state was associated with a varying period of amnesia in all subjects (mean 44 min, SD 36) occurring 15 min after commencement of the loading infusion, and, in two subjects, continuing for 10–20 min after cessation of the whole infusion. Amnesia occurred at a mean CTZ blood concentration greater than 10.3 mg litre⁻¹ (SD 3.8) (table II).

The mean CTZ blood concentration over the last 20 min of infusion and at the cessation of infusion was 7.4 mg litre⁻¹ (SD 2.3), corresponding to a very light degree of sedation only. Recovery was rapid and, by 1 h after infusion, all

<table>
<thead>
<tr>
<th>Subject number</th>
<th>1</th>
<th>2</th>
<th>3*</th>
<th>4</th>
<th>5</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) $C_{\text{max}}$ (mg litre⁻¹)</td>
<td>20.3</td>
<td>18.6</td>
<td>25.1</td>
<td>17.1</td>
<td>11.3</td>
<td>18.5</td>
<td>5.0</td>
</tr>
<tr>
<td>(2) $C_{\text{amnesia}}$ (mg litre⁻¹)</td>
<td>16.2</td>
<td>10.6</td>
<td>10.5</td>
<td>6.9</td>
<td>7.2</td>
<td>10.3</td>
<td>3.8</td>
</tr>
<tr>
<td>(3) $C_{\text{light}}$ (mg litre⁻¹)</td>
<td>9.0</td>
<td>9.2</td>
<td>9.6</td>
<td>6.3</td>
<td>5.5</td>
<td>7.9</td>
<td>1.9</td>
</tr>
<tr>
<td>(4) $C_{\text{end}}$ (mg litre⁻¹)</td>
<td>10.0</td>
<td>6.0</td>
<td>9.7</td>
<td>6.9</td>
<td>4.7</td>
<td>7.4</td>
<td>2.3</td>
</tr>
<tr>
<td>(5) $C_{1-4}$ (mg litre⁻¹)</td>
<td>5.2</td>
<td>2.0</td>
<td>2.5</td>
<td>2.4</td>
<td>1.8</td>
<td>2.8</td>
<td>1.4</td>
</tr>
<tr>
<td>(6) $C_{4-8}$ (mg litre⁻¹)</td>
<td>1.5</td>
<td>0.92</td>
<td>1.3</td>
<td>0.63</td>
<td>0.7</td>
<td>1.0</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table II. (1) = Maximum chlormethiazole (CTZ) blood concentration measured. Values in parentheses indicate maximum concentration predicted from two-compartment model data; (2) = concentration at amnesia; (3) = light sedation occurred; (4) = concentration at end of infusion; (5) = 1 h after infusion; (6) = 4 h after infusion. *Subject 3 was deeply sedated.
subjects were complaining of hunger and were engaged in rational conversation or reading. The mean CTZ blood concentration 1 h after infusion was 2.8 mg litre\(^{-1}\) (SD 1.4).

Derived pharmacokinetic parameters are shown in table III. Total body clearance of chlormethiazole was rapid (mean 1.39 litre min\(^{-1}\), SD 0.58), about one to one-and-a-half times that of indocyanine green (ICG). Renal clearance of chlormethiazole was negligible (mean 1.9 ml min\(^{-1}\), SD 1.1), being less than 0.14% of the total body clearance. The rapid decline in blood concentrations of CTZ immediately following the change from the loading to the maintenance infusion regimen, as well as immediately following cessation of maintenance infusion (fig. 1) reflected a rapid redistribution phase \(T_1^d = 14\) min, table III). This is consistent with the observation that \(V^{\infty}\) was several times \(V_1\) (table III). The mean elimination half-life was 214 min, with considerable variation between subjects (SD 155 min). In three of four subjects in whom ICG clearance was estimated in both the supine and lateral positions, a lower clearance was found in the lateral position. However, there was no statistically significant difference in ICG pharmacokinetics as a function of position. ICG clearance is not synonymous with liver blood flow, which is obtained from the quotient of ICG clearance and ICG extraction ratio with steady-state conditions. However, ICG clearance is a useful reference point for the individual clearance of a flow-limited drug.

All subjects reported nasal irritation, nasal congestion, lacrimation and facial flush 2–5 min after commencement of the infusion. Tachycardia occurred invariably, with a mean increase in heart rate of 34 beat min\(^{-1}\) (SD 10), a 50% increase from the pre-infusion value, 5–10 min after commencing the infusion (fig. 2). This coincided with a moderately sedated state; the heart rate returned to pre-infusion values in all subjects as the degree of sedation lightened (and CTZ blood concentrations

![Figure 2](image-url)
TABLE IV. Metabolite concentrations in blood (read in conjunction with CTZ data in table II). *Approximate concentration only as no authentic reference compound available. Calculated as CTZ. Known to be unstable, hence these values represent minimal values.

<table>
<thead>
<tr>
<th>Metabolite concentration</th>
<th>Subject number</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>AMT</td>
<td></td>
</tr>
<tr>
<td>End of infusion (mg litre$^{-1}$)</td>
<td>0.2</td>
</tr>
<tr>
<td>4 h after infusion (mg litre$^{-1}$)</td>
<td>0.3</td>
</tr>
<tr>
<td>Maximum (mg litre$^{-1}$)</td>
<td>0.3</td>
</tr>
<tr>
<td>Time of maximum (min)</td>
<td>240</td>
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<tr>
<td>Aldehyde metabolite 1*</td>
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<td>End of infusion (mg litre$^{-1}$)</td>
<td>1.8</td>
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<tr>
<td>4 h after infusion (mg litre$^{-1}$)</td>
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<td>Maximum (mg litre$^{-1}$)</td>
<td>3.2</td>
</tr>
<tr>
<td>Time of maximum (min)</td>
<td>145</td>
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</tbody>
</table>

decreased). Before infusion, a change from the supine to the lateral position resulted in a 12% decrease in systolic arterial pressure (SAP) in all subjects (mean 13 mmHg, SD 4). SAP increased during CTZ infusion, with a mean maximum increase of 27% occurring at the end of the initial loading infusion. As sedation lightened, SAP also returned to the pre-infusion values in all subjects.

Two metabolites of CTZ, the secondary alcohol and the ketone, were identified from gas chromatograms of the blood and urine extracts. The retention times for bromethiazole (internal standard), chlormethiazole, secondary alcohol and ketone metabolites were respectively 4.2 min, 2.7 min, 3.7 min and 2.1 min. The blood concentrations of the secondary alcohol metabolite were small (less than 0.1 mg litre$^{-1}$). The ketone metabolite concentration in blood was small compared with that of chlormethiazole (table IV). Another metabolite with a retention time of 3.4 min was present in all blood samples after the commencement of the infusion. Its concentration increased with time up to about 2 h and exceeded that of chlormethiazole (table IV). The retention time corresponded to that of aldehyde also formed by chlormethiazole side-chain oxidation and mass spectral analysis has confirmed this. The aldehyde would be expected to be unstable and it is likely that it was found in blood in the present analysis because of careful cold storage of blood specimens and rapid processing before chromatography.

DISCUSSION
Laborit and colleagues (1957) demonstrated the rapid hypnotic action of CTZ following i.v. injection. The need for large volumes of CTZ to induce anaesthesia and the relatively slow onset of action militated against its usefulness as an induction agent for general anaesthesia. However, its value as a basal sedative and hypnotic in patients undergoing surgery under regional analgesia appears to have been overlooked. Different techniques of CTZ infusion have been suggested to provide supplementation to extradural analgesia. Wilson (1972) suggested induction of anaesthesia using a barbiturate followed by i.v. infusion of 0.8% CTZ to maintain sleep. Schweitzer (1978) used a high loading dose of 20 ml min$^{-1}$ for 3 min to produce sleep, maintaining sleep with an hourly graduated infusion regimen which decreased from 210 to 50 ml h$^{-1}$. In both these studies, extradural blockade was instituted after the onset of sleep. Mather and Cousins (1980) commenced a two-stage infusion based on the administration of 190 ml (1520 mg) over 30 min to induce sleep only after the extradural block was established, followed by a maintenance infusion of 75 ml (600 mg) per hour. Based on the results of these studies and a wider clinical experience, we recommend induction of sedation with CTZ, while the extradural block is being performed to shorten the total time required. This would greatly increase the comfort of the patient during extradural block and probably produce amnesia for the procedure. However, modification of the infusion rates would be required in the aged, others in whom CTZ clearance is diminished (Nation et al., 1976; Pentikainen, Neuvonen and Jostell, 1980), if there was recent administration of sedative or psychotropic drugs and if the degree of sedation was
Amnesia from chlormethiazole has been reported previously (Wilson, 1972; Schweitzer, 1978; Mather and Cousins, 1980) and was found in all of our subjects. Whilst Schweitzer reported complete amnesia extending for several hours following surgery, the period of amnesia in our subjects lasted for the period of infusion, extending to 10–20 min after cessation of infusion in two subjects. However, Schweitzer’s patients were premedicated with papaveretum and hyoscine, and the contribution of hyoscine to the amnesia is difficult to estimate. Premedication certainly does contribute to the quality of sedation during the operation (Gjessing and Tomlin, 1977), while premedication with hyoscine has been shown to contribute to amnesia after operation (Lambrechts and Parkhouse, 1961). Our study in volunteer subjects, without the influence of any other drugs, would suggest that postoperative anterograde amnesia does not result from chlormethiazole infusions if the CTZ blood concentrations decrease to less than about 10 mg litre⁻¹.

The CTZ blood concentration producing this ideal sedated state is similar to that obtained in a previous study by Mather and Cousins (1980), who found that the sleep state occurred at a CTZ blood concentration of 6.7 mg litre⁻¹ base (10.5 mg litre⁻¹ salt). Scott and colleagues (1980) found that unconsciousness was associated with plasma concentrations (base) in the range 3–5 µg ml⁻¹ (5.4–7.8 mg litre⁻¹ salt). This smaller value may have resulted from the poorer physical condition of their patients, who were all undergoing intensive care, and the presence of other sedative and opiate drugs.

Recovery from the effects of chlormethiazole is rapid after short infusions of up to 3 h (Wilson, 1972; Schweitzer, 1978; Mather and Cousins, 1980). This is probably related to the high clearance of the drug (Moore, Triggs et al., 1975; Nation et al., 1976) being one to about one-and-a-half times that of indocyanine green (Seow, Mather and Roberts, 1981). In addition, the high clearance suggests that any systemic disturbances which alter liver blood flow, rather than changes in hepatic metabolism, could increase blood concentrations and exaggerate the clinical effects. High clearance is a desirable property of an i.v. sedative agent as it produces easy control of the depth of sedation and allows rapid awakening on termination of the infusion. Benzodiazepines (Scott, 1975; Gjessing and Tomlin, 1977) and Althesin (Dixon et al., 1976) have been advocated for this purpose. Unfortunately, the benzodiazepines are eliminated slowly: the total body clearance of diazepam is 0.02–0.03 litre min⁻¹ with a half-life of approximately 30 h in normal man (Klotz et al., 1975). Althesin has ideal pharmacokinetic characteristics (high plasma clearance of 1.43 litre min⁻¹) and short elimination half-life (34 min) (Simpson, 1978); but the frequency of hypersensitivity, ranging from 1 : 900 (Watt, 1975) to 1 : 1900 (Evans and Keogh, 1977) must limit its use. Chlormethiazole is suggested as a suitable alternative for short-term sedation for up to a few hours. Prolonged infusion for up to 48 h has been shown to be associated with delayed recovery during intensive care (Scott et al., 1980), but this remains to be confirmed in healthy patients. This suggests cumulative effects from prolonged infusion, and would necessitate the gradual reduction of the rate of infusion to maintain the same degree of sedation. Three metabolites were measured in blood, and these were found to increase in concentration significantly over the period of the study. Whether these metabolites are active in man and contribute to the sedative state during prolonged infusion, warrants further investigation. Reasons for the differences in blood concentrations of HEMT found in the present study and by others (Nation et al., 1977; Tsuei, Thomas and Nation, 1980) are not apparent.

Tachycardia is a recognized feature of chlormethiazole infusion. Wilson, Stephen and Scott (1969) reported an average increase of 48.7% over resting heart rate in volunteers, which is comparable to the 50% in our series, although the heart rate decreased to its pre-infusion value as sedation lightened. The clinical importance of this depends upon the baseline heart rate, but the effect might be useful in the treatment of bradycardia secondary to extradural or spinal analgesia. Galizia, Metreweli and Prout (1975) used chlormethiazole to sedate patients who developed bradycardia as a result of a recent myocardial infarct. Wilson, Stephen and Scott (1969) demonstrated the remarkable stability of mean arterial pressure following chlormethiazole infusion in volunteers. This is contrary to our findings of an increase of 27% in systolic pressure, which was evident once
the patients were moderately sedated. Although Schweitzer (1978) noted stability of arterial pressure following induction of sleep, any effect of chloromethiazole on arterial pressure in that study would be masked by the subsequent institution of extradural blockade.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the invaluable technical assistance of Mr C. McLean, the support of Astra Chemicals Pty Limited (Sydney, Australia), Dr R. L. Nation for the gift of authentic AMT and HEMT and Dr R. G. Moore for pure CTZ and BTZ. Drs D. Topping and R. Ilman of the C.S.I.R.O. Division of Human Nutrition are especially thanked for their willing collaboration on the mass spectrometric studies.

REFERENCES


PERFUSION DE CHLOROMETHIAZOLE EN DEUX TEMPS POUR OBTENIR UNE SEDATION DE BASE

RESUME

Nous avons fait une etude pour determiner l'efficacite du chloromethiazole lorsqu'on souhaitait obtenir une sedation de base, en utilisant une regime de perfusion en deux temps comprenant une dose de charge initiale de 60 mg min⁻¹ pendant 25 min (dans la position laterale), suivie d'une perfusion d'entretien a debit constant de 10 mg min⁻¹ pendant 60 min (dans la position couchee). Ce regime a ete evalue sur cinq jeunes volontaires en bonne sante, lesquels etaient modestement assoupis pendant la plus grande partie de la perfusion, s'endorment lorsqu'on ne les derangeait pas, mais pouvant toutefois etre eveilles facilement pour obeir aux commandements. Nous avons obtenu des periodes d'amen esie variables, correspondant
to a concentration of 10.3 mg litre⁻¹ (standard deviation 3.8)
de chloromethiazole ethanedisulfonate in the blood. It was
detected that a slight sedation occurred during the first 10 min
and the last 20 min of the total perfusion time, corresponding
to concentrations of 7.9 mg litre⁻¹ (standard deviation 1.9)
and 7.4 mg litre⁻¹ (standard deviation 2.3) of chloromethiazole
in the blood. Among the adverse effects, there was a
transient nasal irritation, flushing, and a syndrome resembling
a rhinovirus. Other adverse effects: tachycardia and hypertension,
could be beneficial for neutralizing the cardiovascular depression
associated with central nervous block. We found a high
overall clearance of chloromethiazole (mean 1.39 litre min⁻¹,
standard deviation 0.58) which contributed to the short duration
of action after the cessation of the perfusion.


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INFUSION DE CLOROMETIAZOLA EN DOS FASES
PARA LA SEDACION BASAL

SUMARIO
Se estudió la efectividad de la clorometiazola para proveer
sedación basal, usando un régimen de infusión de dos fases,
consistente de una dosis de carga inicial igual a 60 mg min⁻¹
por espacio de 25 min (en la posición lateral), seguida de una
infusión de mantenimiento de régimen constante igual a
10 mg min⁻¹ por espacio de 60 min (en la posición de supino).
El régimen se evaluó en cinco jóvenes voluntarios y sanos
 quienes sufrieron sedación moderadamente durante la mayor
parte de la infusión, quedándose dormidos al quedarse solos, y
pudiendo despertarse con facilidad para obedecer las órdenes
que se les dieran. Se obtuvieron períodos variables de amnesia
correspondieron con una concentración media de
10.3 mg litro⁻¹ de etanodisulfonato de clorometiazola en la
sangre (Desviación Típica de 3.8). Durante los 10 min iniciales
y durante los últimos 20 min del periodo total de la infusión se
presentó una ligera sedación, correspondiendo a concen-
traciones de 7.9 mg litro⁻¹ (Desviación Típica de 1.9) y de
7.4 mg litro⁻¹ (Desviación Típica de 2.3) de clorometiazola en
la sangre, respectivamente. Los efectos secundarios negativos
fueron la irritación momentánea nasal, el sonrojo de las mejillas
y el síndrome del tipo coriza. Otros efectos secundarios de la
taquicardia y de la hipertensión pueden ser beneficiosos para
contrarrestar la depresión cardiovascular asociada con el
bloqueo neurocentral. Se halló un alto grado de eliminación
de clorometiazola (media de 1.39 litro min⁻¹, Desviación Típica
de 0.58) en el cuerpo y esto contribuiría a la breve duración de la
actividad al término de la infusión.