ASSESSMENT OF THE ANAESTHETIC AND METABOLIC ACTIVITIES OF DIOXYCHLORANE, A NEW HALOGENATED VOLATILE ANAESTHETIC AGENT

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SUMMARY

The ability of dioxychlorane to depress cortical activity in rats with implanted electrodes was compared to that reported previously for methoxyflurane, halothane and enflurane. Dioxychlorane was eight times more potent than enflurane, five times more potent than halothane and twice as potent as methoxyflurane. Serum fluoride concentrations after the administration of dioxychlorane and enflurane were not different from controls. In contrast, serum fluoride concentrations after methoxyflurane reached a value of 105 μmol litre⁻¹ and remained increased for at least the next 48 h. Urine fluoride concentrations in the dioxychlorane and enflurane groups were a half and a quarter, respectively, of those recorded in the methoxyflurane group. Polyuria and polydipsia were observed only in the methoxyflurane group. Dilatation of the proximal convoluted tubules was noted in the rats anaesthetized with methoxyflurane. These changes were most marked at the 6- and 24-h periods following anaesthesia. Haemorrhage and ulcerative cystitis were noted in the bladders of the rats subjected to methoxyflurane. Cellular swelling in the proximal tubule was observed in the rats sacrificed 24 h after the administration of dioxychlorane. Enflurane produced no pathological changes.

Dioxychlorane (4,5-dichloro-2,2-difluoro-1,3-dioxolane; fig. 1) was synthetized in 1975 by Denson, Uyeno and Simon. Preliminary screening in mice suggested that dioxychlorane was an anaesthetic agent. Theoretically, it was expected to be an “inert” gas and, therefore, to exert its biological effects without undergoing chemical transformation during administration and residence in, and elimination from, the body (Denson and Simon, 1976; Denson et al., 1976; Uyeno et al., 1977).

The present study was undertaken to assess the anaesthetic and metabolic activities of dioxychlorane. The anaesthetic activity was investigated by analysing the degree of cortical depression produced in Sprague-Dawley rats with implanted electrodes and comparing these effects with those reported previously (Jaramillo, 1978) for some clinically-employed fluorinated anaesthetics. The metabolic and renal studies were conducted in Fischer 344 rats, a strain which has been reported to be an unusually sensitive model for investigating fluoride-induced nephrotoxicity (Mazze, Cousins and Kosek, 1973). For comparative purposes an equal number of rats was anaesthetized with methoxyflurane or enflurane and, as in the case of dioxychlorane experiments, changes in body weight, food and water intake, urinary and serum fluoride concentrations, volume of urine excreted and histopathological effects on the kidney and bladder were examined.

MATERIALS AND METHODS

Permanent cortical electrodes were placed in 32 male Sprague-Dawley albino rats weighing 100–150 g at the beginning of the experiments. The methods described previously in detail (Jaramillo, 1978, 1979) for the implantation of electrodes and the recording and analysis of the electroencephalograms were followed.

For the metabolic studies, 3-month-old inbred male Fischer 344 rats weighing 180–220 g were used. The animals were placed in individual metabolic cages with food and water allowed ad libitum throughout the experiment. Seven days were allowed for the animals to adapt to their cages. Half of the rats were
pretreated with phenobarbitone to cause enzyme induction (to enhance the metabolism of the anaesthetic agent). The animals were divided into eight treatment groups:

I: Control—normal non-induced rats

II: Control—phenobarbitone-induced rats

III: Dioxychlorane 0.4%, non-induced rats

IV: Dioxychlorane 0.2%, phenobarbitone-induced rats

V: Methoxyflurane 0.5%, non-induced rats

VI: Methoxyflurane 0.5%, phenobarbitone-induced rats

VII: Enflurane 2%, non-induced rats

VIII: Enflurane 2%, phenobarbitone-induced rats

Animals in groups II, IV, VI and VIII received 0.1% phenobarbitone ad libitum in the drinking water for 7 days. Methoxyflurane doses (0.5%, 3 h) were selected to produce moderate renal dysfunction (Mazze, Cousins and Kosek, 1972). Enflurane and dioxychlorane doses were selected to represent concentrations that are approximately equipotent with 0.5% methoxyflurane, according to the data obtained in this study (methoxyflurane 0.5%, dioxychlorane 0.2% and enflurane 2% for a period of 3 h). Control 24-h determinations of body weight, food and water intake and urinary flow were obtained. Daily urinary excretion of inorganic fluoride was monitored with an Orion ion-specific fluoride electrode and a Corning model 110 pH meter.

The anaesthetics were administered in a plastic chamber (50 cm long × 28 cm high × 28 cm wide). Methoxyflurane and dioxychlorane were vaporized in a Pentec 2 and enflurane in a Fluotec 3 vaporizer (both vaporizers were made by Cyprane Ltd, Keighley, Yorkshire). The Pentec 2 vaporizer was calibrated for use with dioxychlorane. The Fluotec 3 vaporizer, originally designed for use with halothane, has been reported (Dobkin et al., 1973) to supply concentrations of enflurane very close to its dial markings. Each anaesthetic was delivered for a period of 3 h. A constant flow (3 litre min⁻¹) of oxygen was delivered as a carrier gas at all times into the vaporizer, the outlet of which was connected to the anaesthetic chamber. The gases were delivered through an inlet port at one end of the anaesthetic chamber and suction was applied to the other end to take up the gases flowing through the chamber. An on-line water manometer monitored the resulting pressures to make certain the gases in the chamber remained at atmospheric pressure.

Anaesthetic concentrations in the chamber were monitored at 30-min intervals by means of a model 7610A Hewlett-Packard gas chromatograph. The gas chromatographic method employed helium as a carrier gas, a flame ionization detector and a 3.6 m × 2.8 cm-i.d. column packed with 15% QF1 maintained at 70 °C. Concentrations were calculated from peak height response compared with a standard curve which was prepared daily. After anaesthesia, the rats received oxygen alone until awake. They were then returned to their individual cages where 24-h body weight, food and water intake and urine collection were continued for the next 7 days.

Serum for inorganic fluoride determinations and kidney and bladder tissues for study by light microscopy were obtained from 52 additional rats treated as those in groups II (n = 4), IV (n = 16), VI (n = 16) and VIII (n = 16). Since no more than eight rats could be anaesthetized at a time, the anaesthetic procedure described above was repeated twice for each anaesthetic. Groups of four animals from each group were sacrificed immediately after anaesthesia and 6, 24 and 48 h later. At the time of sacrifice, the animals were anaesthetized with ether, and 5–6 ml of blood was removed rapidly in a syringe without anticoagulant by puncturing the abdominal aorta. Tissue samples from kidneys and bladders were removed and fixed in Bouin's solution; paraffin sections were prepared and stained with periodic acid–Schiff stain for study by light microscopy. All specimens were coded and examined without knowledge of the animal's treatment.

Statistical analysis

The electroencephalographic data were submitted to analysis of variance of parallel line assay (Finney, 1964). For the metabolic data the mean and SEM of each variable for each rat for the 4 days before anaesthesia were determined and means were calculated for each group. Daily means of postanaesthetic data were computed for each group and compared with the preanaesthetic means. Pre- to post-treatment differences were calculated for each group and intergroup comparisons were made. Paired t tests were used to test the significance of pre- to post-treatment differences within groups.

RESULTS

Effects on the electroencephalogram (e.e.g.)

Dioxychlorane produced changes in the e.e.g. characterized by the presence of spindle-like bursts and irregular, high-amplitude slow waves. As anaes-
DIOXYCHLORANE

Anesthesia deepened, the amplitude of the spindle bursts and the slow-wave activity between bursts became progressively smaller until the burst suppression phase was reached. The intervals of iso-electric activity were prolonged progressively as the amplitude of spike bursts was reduced until the e.e.g. was totally flat in deepest anaesthesia (fig. 2).

This value was obtained by noting the number of times the voltage crossed the zero line in the 3–5-min epoch during which the histogram was recorded. It is, therefore, a measure of the area under the curve of the histogram.

The histogram changes observed during anaesthesia were marked and consisted primarily of a shift of activity toward lower frequencies and a decrease in total activity. Figure 3 shows the baseline interval histogram and those taken 15 min after the administration of increasing concentrations of dioxychlorane. The modal period in the baseline histogram was 20 ms, which corresponds to a frequency of 50 Hz. The histograms taken after the administration of the anaesthetic show differences in several respects. First, there was a notable increase in low frequencies, which was interpreted to mean that the mean frequency of the histogram was less. For the 0.2% concentration, the modal frequency was approximately 40 Hz while those for the 0.42% and 0.67% concentrations were approximately 25 Hz and 20 Hz, respectively. Secondly, with increasing concentrations, there was an increased degree of cortical depression.

Dioxychlorane produced, in a dose-dependent fashion, a decrease in total activity. Figure 4 shows the concentration–response line for dioxychlorane and compares it with those previously reported for methoxyflurane, halothane and enflurane, as obtained 15 min after commencement of anaesthesia. For methoxyflurane, halothane and enflurane the concentration values, as plotted in the x axis, are those dialed in the vaporizer. For dioxychlorane, the concentration values are:

<table>
<thead>
<tr>
<th>Concentration set</th>
<th>Number of samples</th>
<th>Actual concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20%</td>
<td>7</td>
<td>0.18 ± 0.01%</td>
</tr>
<tr>
<td>0.35%</td>
<td>8</td>
<td>0.42 ± 0.02%</td>
</tr>
<tr>
<td>0.50%</td>
<td>9</td>
<td>0.67 ± 0.02%</td>
</tr>
</tbody>
</table>
TABLE I. Comparative relative potencies (±95% confidence limits) of the compounds tested, as assessed over two (0—15 and 0—25 min) time periods. *Data obtained at the end of 15 min of anaesthesia; †data obtained at the end of 25 min of anaesthesia

<table>
<thead>
<tr>
<th>Compound</th>
<th>Enflurane</th>
<th>Halothane</th>
<th>Methoxyflurane</th>
<th>Dioxychlorane</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.53*</td>
<td>3.90*</td>
<td>7.67*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.16—2.00)</td>
<td>(2.90—5.23)</td>
<td>(5.75—10.55)</td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>1.53†</td>
<td>2.55*</td>
<td>5.03*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.06—2.13)</td>
<td>(1.94—3.37)</td>
<td>(3.83—6.83)</td>
<td></td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td>4.03†</td>
<td>2.64†</td>
<td>1.97*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2.73—5.93)</td>
<td>(1.84—3.81)</td>
<td>(1.47—2.72)</td>
<td></td>
</tr>
<tr>
<td>Dioxychlorane</td>
<td>8.43†</td>
<td>5.53†</td>
<td>2.10†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5.80—13.05)</td>
<td>(3.88—8.45)</td>
<td>(1.44—3.26)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4. Concentration–response line obtained for dioxychlorane, as compared with those previously reported for methoxyflurane, halothane and enflurane, 15 min after commencement of anaesthesia.

The parallel line analysis of variance covering all four volatile anaesthetics at the 15- and 25-min periods shows that:

(i) all four compounds evoke a highly significant dose–response relationship;
(ii) all four dose–response relationships are linear;
(iii) all four linear dose–response best-fitted lines are parallel;
(iv) all four lines are statistically different.

When listed in decreasing order of potency, dioxychlorane was the most active, followed by methoxyflurane, halothane and enflurane. Since statistical analysis of the data showed that the concentration–response lines are linear and parallel, relative potency values were calculated. Table I shows the relative potencies (±95% confidence limits) of the four compounds at the 15- and 25-min period after the administration of the drugs.

Table II depicts the recovery values for all of the compounds studied. Recovery values were obtained by measuring the area under the curve for the first 70 min after the withdrawal of the anaesthetic. This value is given as a percentage of the total area. The recovery values for dioxychlorane and methoxyflurane are not statistically different. If the compounds are listed in order according to their rate of recovery, dioxychlorane will be the slowest, followed by methoxyflurane, halothane and enflurane.

Metabolic studies

Cumulative 4-day changes in body weights, food intake, water intake, urinary flow and fluoride excretion. Although plotting of the daily changes in body weight, food intake, water intake, urinary flow and fluoride excretion allows direct comparison of the time-course, onset, peak and duration of the effects of drugs, 4-day
values are in most instances a more precise indication of the overall effect of a particular drug on these variables. Cumulative values in the present study were obtained by adding the values for the 4 “pre-drug” days and the 4 “post-drug” days. Table III shows the Δ values (and their statistical significance when compared with controls) obtained by subtracting the cumulative 4 “pre-drug” day values from the cumulative 4 “post-drug” day values. Control animals (whether treated with phenobarbitone or not) gained weight. All of the animals treated with phenobarbitone lost weight after anaesthesia. Non-induced animals gained weight with the exception of those treated with dioxychlorane (group III), which showed a considerable loss of weight. Variations in food intake among the control animals were not statistically significant. Food intake after anaesthesia was decreased in all treated groups but was statistically highly different (P < 0.001) from control animals only for groups III and VII (dioxychlorane non-induced and enfurane non-induced, respectively). Animals treated with methoxyflurane (groups V and VI) showed an increase in water intake. All of the other animals showed a consistent decrease, especially the non-induced animals anaesthetized with enfurane and dioxychlorane (groups III and VII) in which the decrease in water intake was highly significant when compared with the controls. Similar quantitative results were obtained for the urine volumes. Methoxyflurane was the only anaesthetic to produce the polyuric disorder, particularly in the enzyme-induced animals.

**Toxicity**

All three anaesthetics tested increased significantly the amount of inorganic fluoride present in the urine. That present after methoxyflurane was considerably greater than the fluoruresis after dioxychlorane. Enfurane produced the least effect on the amount of urinary fluoride excreted. Enzyme induction did not appear to modify the amount of fluoride in the urine after enfurane, but it did have an effect after methoxyflurane. In the dioxychlorane group, the phenobarbitone-induced animals received only one-half the amount given to the non-induced, because the phenobarbitone-treated animals did not tolerate anaesthesia with dioxychlorane at a concentration of 0.4%.

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Enzyme induction</th>
<th>Body weight (g)</th>
<th>Food intake (g)</th>
<th>Water intake (ml)</th>
<th>Urinary volume (ml)</th>
<th>Urinary fluoride (μmol litre⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Non-induced</td>
<td>41.30 ± 6.36</td>
<td>2.80 ± 1.23</td>
<td>-1.50 ± 2.31</td>
<td>0.72 ± 1.48</td>
<td>0.68 ± 0.47</td>
</tr>
<tr>
<td>II</td>
<td>Induced</td>
<td>29.17 ± 6.78</td>
<td>-5.67 ± 6.40</td>
<td>0.50 ± 7.83</td>
<td>-3.13 ± 6.46</td>
<td>-1.04 ± 0.82</td>
</tr>
<tr>
<td>Dioxychlorane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Non-induced (0.4%)</td>
<td>-40.00***</td>
<td>-27.00***</td>
<td>-32.11***</td>
<td>-10.10**</td>
<td>19.40***</td>
</tr>
<tr>
<td>IV</td>
<td>Induced (0.2%)</td>
<td>-35.00***</td>
<td>-19.60 n.s.</td>
<td>-32.00**</td>
<td>-1.35 n.s.</td>
<td>20.20***</td>
</tr>
<tr>
<td>Methoxyflurane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Non-induced (0.5%)</td>
<td>11.63**</td>
<td>-1.38*</td>
<td>7.50*</td>
<td>6.75**</td>
<td>44.67***</td>
</tr>
<tr>
<td>VI</td>
<td>Induced (0.5%)</td>
<td>-17.13**</td>
<td>-16.13 n.s.</td>
<td>27.75*</td>
<td>31.93**</td>
<td>56.31***</td>
</tr>
<tr>
<td>Enflurane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>Non-induced (2.0%)</td>
<td>14.56**</td>
<td>-7.00***</td>
<td>-13.44***</td>
<td>-4.87*</td>
<td>3.49***</td>
</tr>
<tr>
<td>VIII</td>
<td>Induced (2.0%)</td>
<td>-4.44***</td>
<td>-8.78 n.s.</td>
<td>-2.00 n.s.</td>
<td>-3.38 n.s.</td>
<td>4.36***</td>
</tr>
</tbody>
</table>

**Table III.** Metabolic effects observed after administration for 3 h of equipotent concentrations of the anaesthetics used. Figures shown are Δ values (cumulative values 4 days after anaesthesia minus cumulative values 4 days before anaesthesia) ± SEM and their statistical significance. *P < 0.05; **P < 0.01; ***P < 0.001 compared with controls. n.s. = not significant. Numbers in parentheses indicate the vapour concentration administered to each group
While increases in the fluoride concentrations were found in the urine following the administration of all three anaesthetics, only the rats receiving methoxyflurane showed increased concentrations of inorganic fluoride in the blood. After 3 h of anaesthesia with 0.5% methoxyflurane, the serum fluoride concentrations increased from a control value of 17 μmol litre⁻¹ to 105 μmol litre⁻¹. The concentrations of serum fluoride after dioxyclocharane and enflurane were not significantly different from those found for the control animals. Serum fluoride concentrations after methoxyflurane remained increased for several days. Fortyeight hours after anaesthesia with methoxyflurane, the concentration of serum inorganic fluoride was still as great as 38 μmol litre⁻¹.

Light microscopy of the renal cortices of rats anaesthetized with methoxyflurane showed widespread dilatation of the proximal convoluted tubules. The height of the single layer of cuboidal cells composing the proximal tubule appeared to be reduced. However, nuclear alterations such as pyknosis or karyorrhexis were not present. A few foci of intraluminal sloughing of necrotic tubular epithelial cells were observed. The glomeruli were normal. The tubular changes were most marked at the 6- and 24-h periods after anaesthesia. Evidence of some tubular regeneration was seen in the 48-h group. Examination of the bladder of rats sacrificed 6 and 24 h after receiving methoxyflurane showed severe haemorrhagic and ulcerative cystitis. The bladders of the other rats receiving methoxyflurane were normal.

Rats receiving dioxyclocharane and sacrificed 24 h later showed cellular swelling most notable in the proximal convoluted tubules. Some tubular changes were seen after dioxyclocharane which resembled those described for methoxyflurane, but they were fewer in number and there was no evidence of necrosis. The bladders of these rats were normal. In comparison with the methoxyflurane experiments, dioxyclocharane was markedly less nephrotoxic under the conditions of the study.

Rats anaesthetized with enflurane showed no pathological changes in the kidney or bladder as compared with the controls.

**DISCUSSION**

Dioxyclocharane was found to produce changes in the e.e.g. that are characteristic of commonly-used inhalation anaesthetics. Dioxyclocharane produced no unusual patterns of c.n.s. excitation. In contrast, such patterns are seen readily with enflurane at concentrations slightly greater than those used to induce anaesthesia. In respect of potency, dioxyclocharane appears to be the most active known inhalation anaesthetic. Its potency ranges from 2 to 3 times that of methoxyflurane, the most potent of the currently-used inhalation anaesthetics. When compared with agents that have been considered recently for clinical use, dioxyclocharane is considerably more potent than sevoflurane (Wallin et al., 1975) and aliflurane (Steen, Burgstedt and Holaday, 1976). The parallelism of the linear dose–response lines observed for all four compounds may indicate that these anaesthetic agents possess a similar mechanism of action in depressing brain activity. In this regard, it is interesting to note that the relative potency value for the 0–15-min period of anaesthesia is very similar to that for the 0–25-min period, for all of the compounds studied. A close relationship was found between potency and rate of recovery for the four anaesthetic agents tested. Therefore, the recovery from anaesthesia of animals under dioxyclocharane was significantly slower than that for halothane and enflurane, but not statistically different from that observed for methoxyflurane.

Following exposure to anaesthetic concentrations of dioxyclocharane, non-induced Fischer 344 rats showed significant decreases in body weight and food and water intake. Similar results were recorded in the methoxyflurane and enflurane experiments. The body weights after dioxyclocharane were significantly less than those observed during the period before treatment for the same group of animals. The rate of growth for the animals receiving enflurane and methoxyflurane was decreased as compared with that of the controls, but these animals (in contrast to those receiving dioxyclocharane) gained some weight in the period following anaesthesia. The food intake of all of the animals receiving anaesthesia was decreased in the period after anaesthesia as compared with the period before anaesthesia. This decrease was substantially greater for the dioxyclocharane-treated animals. Contrary to the methoxyflurane group, all of the animals receiving either enflurane or dioxyclocharane decreased their water consumption after anaesthesia.

In rats anaesthetized with methoxyflurane, statistically significant increases in urine volume and in serum and urinary inorganic fluoride concentrations occurred. However, following dioxyclocharane and enflurane exposures in concentrations equipotent to that of methoxyflurane, urinary fluoride excretion
during the first 4 days following anaesthesia was only 1/2 and 1/4, respectively, that of methoxyflurane. Moreover, neither polyuria nor polydipsia was observed in the animals exposed to dioxychlorane or enflurane. The threshold value for causing an untoward polyuria in Fischer 344 rats has been estimated to be 50 μmol litre⁻¹ of serum inorganic fluoride (Cook et al., 1975). Once this value is exceeded the severity of the nephrotoxicity depends primarily upon the degree of increase and the duration for which increased concentrations of serum fluoride are maintained (Cousins et al., 1974). Subclinical renal toxicity has been reported to occur following methoxyflurane at serum inorganic fluoride concentrations of 50 μmol litre⁻¹, while clinical toxicity has been seen in patients in whom the serum inorganic fluoride exceeded 90 μmol litre⁻¹ (Cousins and Mazze, 1973). Although the present study demonstrates that defluorination of the three anaesthetics took place in all of the animals (as indicated by increased urinary inorganic fluoride concentrations), the extent of increased defluorination following dioxychlorane and enflurane was considerably less than that seen with methoxyflurane. More important, peak serum fluoride concentrations after dioxychlorane and enflurane anaesthesia were not different from those obtained in control animals, whereas following methoxyflurane anaesthesia, serum fluoride concentrations peaked markedly and immediately after anaesthesia and then decreased very slowly. The prolonged increase of serum fluoride following administration of methoxyflurane or sodium fluoride has been associated with nephrotoxicity not only in animals (Frascino et al., 1972; Mazze, Cousins and Kosek, 1972, 1973; Bell, Hitt and Mazze, 1975; Brodeur et al., 1976), but also in humans (Taves et al., 1970; Mazze, Trudell and Cousins, 1971; Cousins and Mazze, 1973). As in man, the syndrome of renal dysfunction in our experiments was characterized, in the case of methoxyflurane, by polyuria. In contrast, dioxychlorane anaesthesia produced only a moderate, short-lasting increase in inorganic fluoride concentration in the urine and no increase in the urine volume or in the amount of fluoride in the serum. The nephrotoxic liability of dioxychlorane, although much less than methoxyflurane, is probably not absolute—especially when used in prolonged anaesthesia. Serum inorganic fluoride concentration, urinary volume and urinary fluoride excretion have been shown to increase with the total time that the animals are subjected to the anaesthetic (Uyeno et al., 1977). The degree of maximum polyuria and peak inorganic fluoride excretion has been reported by Barr and coworkers (1974) to be similar in animals receiving 2.5% enflurane for 10 h and those receiving 0.25% methoxyflurane for 1.5 h. However, serum fluoride concentrations in these investigators’ enflurane group of animals at 24 h was only 16.0 μmol litre⁻¹ in contrast to 65.7 μmol litre⁻¹ in the group receiving methoxyflurane.

The present study shows that enzyme induction following phenobarbitone administration resulted in an increase in the metabolism of dioxychlorane. Enzyme induction in man as a result of exposure to various chemical substances such as barbiturates, tranquillizers, insecticides and aerosol sprays may exacerbate renal toxicity. Repeated administration of dioxychlorane may impose an increased risk of toxicity because of enzyme induction and residual concentrations of inorganic fluoride. Other factors may influence the toxicity of dioxychlorane adversely; for example, there appears to be a marked variation in the susceptibility of different individuals to fluoride as a nephrotoxin and a marked individual variation in metabolism of some anaesthetics for the same administered dose, resulting in markedly different serum inorganic fluoride concentrations (Cousins and Mazze, 1973).

Histopathological changes in the kidney in this study were considerably more pronounced in the group of animals anaesthetized with methoxyflurane than those given dioxychlorane or enflurane. A marked increase in urinary volume and pronounced histopathological changes indicated more renal damage in the methoxyflurane group than in the other groups. The occurrence of haemorrhagic cystitis in the methoxyflurane group has been reported previously by Mazze, Cousins and Kosek (1972). A similar frequency of this complication occurred after prolonged isoflurane (Cousins et al., 1973) and enflurane (Barr et al., 1974) anaesthesia in Fischer 344 rats. Haemorrhagic cystitis after these anaesthetics has not been reported in man and probably represents a species or organ-specific toxicity.

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REFERENCES


EVALUATION DES ACTIVITÉS ANESTHÉSIQUES ET METABOLIQUES DU DIOXYCHLORANE, UN NOUVEL AGENT ANESTHESIANT HALOGENÉ ET VOLATIL

RESUME

La faculté que possède le dioxychlorane de déprimer l'activité corticale des rats auxquels on a implanté des électrodes, a été comparée à celle que l'on avait précédemment signalée pour le méthoxyfluorane, l'halothane et l'enflurane. Le dioxychlorane est huit fois plus puissant que l'enflurane, cinq fois plus puissant que l'halothane et deux fois plus puissant que le méthoxyfluorane. Les concentrations de fluorure dans le sérum, après l'administration de dioxychlorane et d'enflurane, n'ont pas été différentes des valeurs témoin. Par contre, après l'administration de méthoxyfluorane, les concentrations de fluorure dans le sérum ont atteint une valeur de 105 µmol litre⁻¹ et sont restées fortes pendant au moins 48 heures suivantes. Les concentrations de fluorure dans l'urine, que l'on a trouvées dans les groupes traités au dioxychlorane et à l'enflurane, ont été de 1 et 1,5 respectivement de celles enregistrées pour le groupe traité au méthoxyfluorane. On n'a observé de la polyurie et de la polydipsie que dans le groupe traité au méthoxyfluorane. On a remarqué une dilatation des tubes contournés proximaux chez les rats anesthésiés au méthoxyfluorane. Ces changements ont été particulièrement marqués entre 6 et 24 h après l'anesthésie. On a remarqué une hémorragie et une cystite ulcéreuse dans la vessie des rats traités au méthoxyfluorane. Une enflure cellulaire du tube proximal a été observée chez les rats sacrifiés 24 h après l'administration de dioxychlorane. L'enflurane n'a causé aucun changement pathologique.

BEWERTUNG DER ANÄSTHETISCHEN UND STOFFWECHSEL-WIRKUNGEN VON DIOXYCHLORAN, EINEM NEUEN, HALOGENIEREN NARKOSEMITTEL

ZUSAMMENFASSUNG

Die Fähigkeit von Dioxychloran zur Unterdrückung der kortikalen Aktivität in Ratten mit eingepflanzten Elektroden wurde mit der schon berichteten Wirkung von Methoxyflower, Halothan und Enfluran verglichen. Dioxychloran war 8× stärker als Enfluran, 5× stärker als Halothan und

EVALUACION DE LAS ACTIVIDADES ANESTETICAS YMETABOLICAS DEL DIOXICLORANO, UN NUEVO AGENTE ANESTETICO VOLATIL HALOGENADO

SUMARIO
Se procedió a la comparación de la capacidad del dioxiclorano para deprimir la actividad cortical en ratones a los cuales se insertaron electrodos, con la capacidad previamente indicada para el metoxifluran, el halotano y el enfluran. El dioxiclorano tiene una potencia ocho veces mayor de la del enfluran, cinco veces mayor de la del halotano y dos veces mayor de la del metoxifluran. Las concentraciones de fluoruro en el sero después de la administración de dioxiclorano y de enfluran no diferían de las de los controles. En cambio, las concentraciones de fluoruro en el sero después de la administración de metoxifluran alcanzaron un valor de 105 µmol litre⁻¹ y permanecieron así durante las siguientes 48 h por lo menos. Las concentraciones de fluoruro en la orina en los grupos de dioxiclorano y de enfluran eran de 1/3 y de 1/4 respectivamente en relación con las concentraciones registradas en el grupo del metoxifluran. Se observaron poliuria y polidipsia en el grupo de metoxifluran única. Se notó una dilatación de los túbulos convolutados proximales en los ratones anestesiados con metoxifluran. Estos cambios fueron particularmente marcados en los periodos de 6 y 24 h después de la anestesia. Se registró hemorragias y cistitis ulcerante en las vejías de los ratones sometidos a anestesia por metoxifluran. Se observó inchaón celular en el tubulo proximal de los ratones beneficiados 24 h después de la administración de dioxiclorano. El enfluran no produjo ningún cambio patológico.