EVALUATION OF DOXAPRAM FOR AROUSAL FROM GENERAL ANAESTHESIA IN OUTPATIENTS

G. S. ROBERTSON, D. M. MACGREGOR AND C. J. JONES

SUMMARY
In a double-blind study of 100 outpatients receiving methohexitone, nitrous oxide and halothane, the administration of doxapram 80 mg i.v. was associated with a significantly more rapid recovery from anaesthesia, the effect being more obvious in women than men. Doxapram produced a reduction of 3-4 min in the time of recovery to a safe level of consciousness. The effect was probably a result of the more rapid elimination of halothane caused by stimulation of respiration. In the patients who received doxapram the incidence of minor complications during recovery was reduced and there was some evidence of an improvement in the quality of recovery.

After reviewing the differences of opinion regarding the arousal effect of doxapram (Dopram, A. H. Robins Ltd) following general anaesthesia, Gupta and Dundee (1973), in a study of 40 patients, showed that the injection of doxapram produced a significantly shorter mean arousal time than did a placebo. Their investigation was carried out double-blind in female patients premedicated with pethidine and atropine, and in whom anaesthesia was induced with thiopentone; at the end of anaesthesia, all patients being unconscious and unresponsive, doxapram 1 mg/kg was given i.v.

In a comment on the study of Gupta and Dundee, Hamilton (1974) indicated that while it provided information regarding the pharmacology of doxapram, it did not “provide evidence for use of the drug in the clinical situation”. Although Gupta and Dundee recommended further studies using doxapram as a continuous infusion, it seemed appropriate to make a practical evaluation of its arousal effect in unpremedicated patients; this would reduce the number of variable factors and might permit conclusions relevant and possibly beneficial to outpatient anaesthesia. In view of the more rapid recovery from methohexitone compared with thiopentone (Carson, Graham and Dundee, 1975) and its wide acceptance for outpatient anaesthesia, the present study was designed to assess the effect of doxapram on recovery from a sequence of methohexitone, nitrous oxide and halothane in outpatients.

METHOD
One hundred patients aged 70 yr or less, attending a genito-urinary outpatient clinic were studied. The anaesthetic sequence was standard, apart from variations in the dose of methohexitone according to the sex of the subjects. Female patients received methohexitone 80 mg, male patients received 90 or 100 mg, given i.v. rapidly as a 1% solution, using an indwelling needle in the dorsum of the hand. Nitrous oxide 6 litre and oxygen 3 litre were then administered, together with halothane 0.5%, and carbon dioxide 500 ml which was given to promote the uptake of halothane. The concentration of halothane was increased gradually but, because of the potential hazards of halothane in conjunction with carbon dioxide, when an inspired concentration of 2% halothane had been reached the carbon dioxide was discontinued. At the beginning of exposure to halothane a stop-watch was started and, after the maximum necessary concentration of halothane had been reached, anaesthesia was maintained with a reducing concentration with the aim of having all patients breathing 0.5% halothane at the end of surgery. The duration of exposure to halothane was noted. The administration of nitrous oxide and oxygen was continued for a further 30 s during which 2 ml of a solution from a coded ampoule (allocated by random numbers) was given i.v., followed by a further 2 ml for 30 s while 100% oxygen was administered. The solution was either doxapram 20 mg/ml or normal saline; neither of the investigators knew the nature of the solution.

When halothane was discontinued, the stop-watch was re-set for the measurement of recovery time. This was assessed at 1-min intervals for 8 min and again at
10 min. Recovery was assessed by the following scoring system:

**Consciousness**

- Fully awake; eyes open; conversing: Score 4
- Lightly asleep; eyes open intermittently: Score 3
- Eyes open on command or in response to name: Score 2
- Responding to ear-pinching: Score 1
- Not responding: Score 0

**Airway**

- Opening mouth or coughing or both, on command: Score 3
- No voluntary cough, but airway clear without support: Score 2
- Airway obstructed on neck flexion but clear without support on extension: Score 1
- Airway obstructing without support: Score 0

**Activity**

- Raising one arm on command: Score 2
- Non-purposeful movement: Score 1
- Not moving: Score 0

The scoring system was designed to emphasize the maintenance of a clear airway and the awake state, these being essential for patient safety with the minimum of nursing supervision. The system was designed to be more sensitive than that of Gupta and Dundee (1973) and incorporated certain features of the scoring system suggested by Steward (1975) for use in the recovery room. In the present study a recovery score of 9 indicated complete recovery to the awake state. All 100 anaesthetics were administered by the same investigator while another conducted all of the assessments.

The surgical procedures were:

**Doxapram group**

- Cystoscopy 18
- Cystoscopy plus a minor procedure 27
- Urethral dilatation 4
- Vasectomy 1

![Graph showing mean recovery scores and SEM in doxapram-treated and control male patients.](image-url)
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Fig. 2. Mean recovery scores and SEM in doxapram-treated and control female patients.

Control group
- cystoscopy 20
- cystoscopy plus a minor procedure 27
- vasectomy 3

Statistical methods
The results were analysed using the Chi-squared test. Further analysis of the recovery features in male and female patients was carried out by the "odds ratio" method (Clayton, 1974). The odds ratio analysis of ordered categorical data expresses the odds of an all-or-none event occurring in one group compared with another group. For example, in our study, taking consciousness as any value of the score greater than 0 the following results were obtained at 2 min:

<table>
<thead>
<tr>
<th></th>
<th>Doxapram</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconscious</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>Conscious</td>
<td>31</td>
<td>10</td>
</tr>
</tbody>
</table>

Thus, the odds of being "conscious" at 2 min in the doxapram group were $31/19 = 1.63$; the odds of being "conscious" in the control group were $10/40 = 0.25$. This gives an odds ratio of $1.63 : 0.25 = 6.53$. In our scoring system there are four possible definitions of "consciousness" and thus there are four possible odds ratios; each ratio can be weighted in relation to statistical reliability and from the weighted odds ratios the "mean odds ratio" can be calculated.

RESULTS
The mean values of basic data in the doxapram-treated and control groups are shown in table I. The male patients were about 10 kg heavier than the females, and between the female groups there was a substantial difference in the duration of exposure to halothane. Mean values for recovery scores at each
assessment time are illustrated in figures 1 and 2. The data on recovery (table II) indicate that there was a statistically significant difference in favour of doxapram in the early stages and up to the 7th min. Comparing all three features in male and female patients, there was a significantly more rapid recovery in the doxapram-treated group in the first 5 min ($P < 0.001$ for consciousness at 2 min).

The mean odds ratios in favour of doxapram are shown in table III and there is an obvious greater response in females in the first few minutes. Figures 3 and 4 illustrate the mean odds ratios in favour of females, showing the marked difference between male and female recovery patterns in patients receiving doxapram. A later increase in mean odds ratio in favour of females is evident in the doxapram-treated and control groups. Figure 5 shows the median consciousness scores for male and female patients in both study groups and illustrates the more rapid recovery of females in the control group and the acceleration of the normal recovery pattern produced by doxapram in both sexes.

Correlation coefficients relating recovery scores within each sex group to age, body weight, dose of methohexitone and duration of exposure to halothane were not significant. Retrospective comparison of the dose of doxapram related to body weight showed that women had received an average of 1.32 mg/kg, whereas men had received 1.13 mg/kg.

<table>
<thead>
<tr>
<th>TABLE I. Data of the patients in the study—mean values</th>
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<tbody>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Doxapram</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Halothane (s)</td>
</tr>
<tr>
<td>Methohexitone (mg)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE II. P values for Chi-squared analysis comparing recovery features in doxapram-treated and control patients</th>
</tr>
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<tbody>
<tr>
<td>Time (min)</td>
</tr>
<tr>
<td>Cons.</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<td>5</td>
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<tr>
<td>6</td>
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<tr>
<td>7</td>
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<tr>
<td>8</td>
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<tr>
<td>10</td>
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Cons. = consciousness; n.s. = not significant.
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TABLE III. Values of mean odds ratios of doxapram-treated patients relative to control patients for each feature of the recovery score

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Consciousness</th>
<th>Airway</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male Female</td>
<td>Male Female</td>
<td>Male Female</td>
</tr>
<tr>
<td>2</td>
<td>3.51 17.99</td>
<td>1.27 17.82</td>
<td>0.32 27.17</td>
</tr>
<tr>
<td>3</td>
<td>2.70 6.52</td>
<td>2.03 7.41</td>
<td>0.83 7.23</td>
</tr>
<tr>
<td>4</td>
<td>3.15 7.69</td>
<td>3.84 5.49</td>
<td>3.16 3.49</td>
</tr>
<tr>
<td>5</td>
<td>4.47 7.09</td>
<td>7.30 8.24</td>
<td>6.57 3.61</td>
</tr>
<tr>
<td>6</td>
<td>4.85 5.76</td>
<td>3.49 1.89</td>
<td>5.47 1.17</td>
</tr>
<tr>
<td>7</td>
<td>3.86 3.38</td>
<td>2.67 2.02</td>
<td>2.34 1.32</td>
</tr>
<tr>
<td>8</td>
<td>3.90 2.21</td>
<td>3.93 —</td>
<td>7.74 —</td>
</tr>
<tr>
<td>10</td>
<td>2.70 2.02</td>
<td>— —</td>
<td>3.17 —</td>
</tr>
</tbody>
</table>

Side-effects in the first 10 min after anaesthesia were noted, none being serious. In the doxapram-treated group seven patients developed minor sequelae: excessive coughing (3), weeping (2), muscle tremor (1) and nausea together with a hysterical reaction to dreaming (1). Minor problems were noted in 12 of the control patients: coughing (4), weeping (5), excessive sweating (1), excessive salivation (1) and vomiting (1). One patient in the doxapram-treated group developed nausea and vomiting after leaving the recovery area.

DISCUSSION

Because of the design of this study, a relatively small number of female patients received doxapram in comparison with the control groups and the male groups; also the pattern of recovery was quite different when the male and female treated groups were compared. Therefore, separation of the results for each sex was necessary in the statistical analysis. The effect of doxapram in female patients was obvious as early as 2 min after termination of the anaesthetic, and consciousness scores were obtained with doxapram which were not achieved until about 3 or 4 min later in the control patients (fig. 5). In men, the peak effect of doxapram occurred at 5 min and the sex difference in the speed of recovery is probably explained by the higher dose of doxapram in relation to body weight in women. However, within the male and female treated groups there was no clear inverse correlation between body weight and the rate of recovery. Presumably, the marked difference between the male and female responses would have been even more obvious had not the randomization allocated 52% of women to the control group and 32% to the doxapram group; thus the overall result is achieved despite an in-built bias against doxapram.

The improved rate of recovery in the doxapram-treated patients is similar to that described by Gupta and Dundee (1973) but direct comparison is not possible because of the different dose of doxapram used by these workers (1 mg/kg), the different scoring system and the fact that the study was conducted only in patients who were deeply unconscious at the 2nd min after anaesthesia.

The anaesthetic technique in the present study differed from the normal for outpatients in that recovery was timed from the moment of stopping halothane administration instead of the more usual technique of employing only nitrous oxide with oxygen for the last 1 or 2 min of a surgical procedure. However, it was considered necessary to time recovery from a reproducible starting point. It is reasonable to assume that in more normal clinical usage, recovery times in all groups would have been

![Fig. 4. Logarithmic scale representation of mean odds ratios in favour of females related to time after termination of anaesthesia in control patients.](image-url)
FIG. 5. Median consciousness scores in doxapram-treated and control groups of male and female patients after the termination of anaesthesia.

shorter. From the point of view of nursing supervision of recovering patients, there is a clear benefit in obtaining a more rapid return to safe levels of consciousness, and this study suggests that the use of doxapram in suitable dosage may permit a worthwhile reduction of recovery time. Whilst a recovery score of 9 indicated complete recovery to the awake state, a score of 7 reflected the return to a safe level of consciousness, the patient being lightly asleep and maintaining a clear airway without support. The scoring system was simple, sensitive and unequivocal in use, and scoring even on the “consciousness” feature alone gives a reliable overall index of safety and demonstrates the clear effect of doxapram: figure 5 shows that doxapram produced recovery to the point at which the eyes were opened on command (consciousness score 2) at about 4 min earlier than occurred in the control groups.

There was no tendency for the doxapram-treated patients to lapse back into sleep. A pleasant recovery with relative absence of side-effects was a feature of the doxapram group; one patient, a doctor, remarked spontaneously about the pleasantness of his recovery compared with 10 previous anaesthetics, referring to the absence of the “drifting” sensation of previous recoveries. The increased alertness of patients after doxapram administration was noted by Evers and Dobkin (1967), who also commented that the use of doxapram could have allowed much earlier discharge of patients from the recovery room. Winnie and Collins (1966), studying the effect of doxapram on ventilation, remarked that in addition to the arousal effect of doxapram there was a clear reduction of side-effects when compared with the action of ethamivan, bemegride and nikethamide.

One of the principal effects of doxapram is respiratory stimulation, largely as a result of its effect on the carotid chemoreceptors (Hirsh and Wang, 1972, 1974; Mitchell and Herbert, 1975). It is likely that the more rapid arousal from anaesthesia described in this study
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can be explained by the more rapid elimination of halothane caused by increased ventilation.

Whether doxapram has a separate and more direct arousal effect by cortical or medullary excitation is uncertain. Two clinical studies suggested that doxapram could effect a reduction in recovery time following i.v. anaesthesia alone (Siker, Mustafa and Wolfson, 1964; Po, Watson and Hansen, 1968) but Evers and Dobkin (1967), while finding a better quality of recovery associated with doxapram following thiopentone anaesthesia, failed to demonstrate significantly shorter awakening times.

In the present study, the more rapid recovery of women in the doxapram-treated and control groups when compared with men is of interest. It is not related to the comparative dose of methohexitone which is slightly greater in relation to body weight in women than in men. Likewise there is no apparent relationship with the mean duration of exposure to halothane, which is greatest in the doxapram-treated women. The results may reflect some difference in the early distribution of methohexitone in the body as a result of the relatively higher proportion of adipose tissue in women.

ACKNOWLEDGEMENTS

We thank Mr W. H. H. Garvie and Mr J. Steyn for permitting this study to be conducted on their patients and Messrs A. H. Robins Ltd for supplying the coded ampoules of doxapram and saline. We thank also Mr D. Clayton, Department of Clinical Epidemiology, The Royal Free Hospital, London, for advice on the evaluation of results and for conducting the statistical evaluations.

REFERENCES


EVALUATION DU DOXAPRAM POUR LE REVEIL D'UNE ANESTHESIE GENERALE SUR DES MALADES DE CONSULTATION EXTERNE

RESUME

Dans une étude à double inconnue effectuée sur 100 malades de consultation externe recevant du méthohexiton, du protoxyde d'azote et de l'halothane, l'administration intraveineuse de 80 mg de doxapram a été associé à un réveil beaucoup plus rapide de l'anesthésie, cet effet étant plus évident chez les femmes que chez les hommes. Le doxapram a entraîné une réduction de 3 à 4 min dans le temps nécessaire au réveil à un niveau sûr. Cet effet est probablement le résultat d'une réduction plus rapide de l'halothane par suite de la stimulation de la respiration. Sur les malades qui avaient reçu du doxapram, l'incidence de complications mineures pendant le réveil a été plus faible et il y a même eu quelque évidence d'une amélioration dans la qualité du réveil.

BEURTEILUNG VON DOXAPRAM FÜR DIE ERWECKUNG VON AUßENPATIENTEN AUS DER VOLLNARKOSE

ZUSAMMENFASSUNG

In einer Doppelblinduntersuchung von 100 Aussenpatienten, die Methohexiton, Stickstoffoxydul und Halothan erhielten, war die intravenöse Verabreichung von 80 mg Doxapram mit einer bedeutend schnelleren Erholung aus der Narkose verbunden, wobei die Wirkung bei Frauen deutlicher war, als bei Männern. Doxapram bewirkte eine Verminderung von 3–4 Minuten in der Erholungszeit bis zu einem gefährlosen Bewusstseinsniveau. Der Effekt war wahrscheinlich ein Ergebnis der schnelleren Halothan-Ausscheidung infolge der Atmungssimulation. Bei den Doxapram erhaltenden Patienten war das Vorkommen geringfügiger Komplikationen während der Erholung zurückgegangen, und es wurde eine gewisse Verbesserung in der Erholungsqualität festgestellt.

EVALUACION DEL DOXAPRAM PARA LA RECUPERACION TRAS ANESTESIA GENERAL EN PACIENTES AMBULANTES

SUMARIO

En un estudio a doble ciego de 100 pacientes en régimen ambulatorio que recibieron metohexitona, monóxido de
nitrogeno y halotano, la administración del doxapram (80 mg endovenosamente) fue asociada con una recuperación significativamente más rápida tras la anestesia; el efecto fue más evidente en las mujeres que en los hombres. Doxapram produjo una reducción de 3–4 min en el tiempo de recuperación a un nivel seguro de consciencia. El efecto probablemente se debió a la más rápida eliminación del halotano causada por estimulación de la respiración. En los pacientes que recibieron doxapram la frecuencia de complicaciones menores durante la recuperación fue disminuida y hubo cierta evidencia de una mejora en la calidad de la recuperación.