Reduction of the Psychotomimetic and Circulatory Side-effects of Ketamine by Droperidol

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The effects of four centrally-acting drugs on the incidence and severity of emergence phenomena associated with ketamine anesthesia were investigated in a double-blind study. Two hundred and fourteen outpatients scheduled for early elective termination of pregnancy were premedicated with atropine and randomly divided into five groups. Anesthesia of all patients was induced with ketamine, 2.5 mg/kg, and maintained with fractional doses of ketamine. The drugs studied were: diazepam, 150 μg/kg; thiopental, 1.5 mg/kg; droperidol, 75 μg/kg; fentanyl, 0.375 μg/kg. Droperidol alone or in combination with fentanyl significantly decreased the incidences of restlessness, crying, screaming, and hallucinations associated with recovery from ketamine anesthesia. Diazepam and thiopental were ineffective. Droperidol or droperidol and fentanyl also decreased ketamine-induced tachycardia and hypertension.

None of the drugs studied delayed recovery from anesthesia and the discharge of patients. (Key words: Diazepam; Droperidol; Fentanyl; Hallucinations; Ketamine; Psychotomimetic; Thiopental.)

It had been reported that induction of anesthesia with ketamine hydrochloride (Ketalar: Ketavect) is accompanied by significant, transient increases of pulse rate and blood pressure, and that emergence from ketamine anesthesia is frequently complicated by disturbing psychomotor (e.g., incoordinated movements) and psychotomimetic manifestations, such as screaming, crying, disorientation, and visual hallucinations. On occasion the hallucinations can be terrifying and may be followed by “nightmares” for several days or weeks. These disturbing emergence phenomena are more frequent and more severe in adolescents and young to middle-aged adults than in children or in the aged. The unpredictable incidence and severity of emergence phenomena and the hostile reaction of patients to their postanesthetic experience has greatly restricted the use of this otherwise-useful agent.

The purpose of this study was to determine whether ketamine-induced tachycardia, hypertension, and psychotomimetic effects could be suppressed by the concomitant use of other central nervous system depressants.

Materials and Methods

The subjects of the study were 214 outpatients undergoing early elective termination of pregnancy (abortion). All patients were premedicated with 0.4 to 0.6 mg atropine sulfate, administered intramuscularly 30 to 45 min before the start of anesthesia. Ketamine, 2.5 mg/kg, was administered over a 30-sec period in an intravenous infusion of 5 per cent dextrose in water. Subsequent 0.5-mg/kg doses of ketamine were administered as necessary. All patients breathed room air. Most patients also received 0.2 mg methylergogonovine maleate (Methergine), or 10 USP units of oxytocin (Pitocin), or both.

Pulse rate and systolic and diastolic blood pressure, measured by auscultation, and respiratory rate were recorded with the patient seated and supine before she was taken to the

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operating room; in the operating room, these values were measured in the lithotomy position, just before the start of ketamine injection; 2, 5, and 10 min after the start of ketamine, and at the end of operation. The measurements were made again, with the patient seated and supine in the recovery room before discharge, to ensure that there was no danger of orthostatic hypotension.

The study was carried out in two phases. In the first phase 192 consecutive patients were randomly assigned to four groups. Group A, 31 patients, received ketamine only; Group B, 30 patients, and Group C, 31 patients, were given 150 µg/kg diazepam (Valium) or 1.5 mg/kg thiopental sodium (pentothal), respectively, at the end of operation. The 31 subjects of Group D were given 75 µg/kg droperidol (Inapsine) 6 min before induction of ketamine anesthesia. All drugs were given intravenously. Results of the first phase of this study indicated that droperidol, but not diazepam or thiopental, decreased the incidence and severity of emergence phenomena.

Because of the small number of subjects, the difference in the first phase of the study were not statistically significant. Therefore, in the second phase 92 subjects were randomly assigned to three groups. Thirty received ketamine alone; 30, ketamine preceded by 75 µg/kg droperidol; 32 (Group E) were given 75 µg/kg droperidol and 0.375 µg/kg fentanyl lactate (Sublimaze) 6 min before induction.

All anesthesia was administered by two anesthesiologists who also recorded all observations before and after anesthesia. The postanesthetic courses were observed by two other anesthesiologists who had no knowledge of the doses of ketamine or the supplementary drugs administered. These data were entered on the postanesthetic observation sheets after termination of the study.

Patients were allowed to recover undisturbed. Recovery was assumed to be complete when the patient responded to a quiet "good morning" and was oriented in time and space. The time between the last administration of ketamine and recovery of consciousness was recorded. The occurrence of restlessness and/or incoordinated movements, crying, screaming, and vomiting during recovery was also recorded. Immediately after recovery the observer noted whether, in his opinion, the patient was calm and alert, calm and sleepy, agitated, or frightened. At this time, and again three hours after administration of the last dose of ketamine, the patients were questioned as to the presence of sleepiness, dizziness, generalized weakness, headache, abdominal pain, and hallucinations. Recall of hallucinations at the time of discharge was noted also. Since the preanesthetic and anesthetic managements of Groups A, B, and C were identical, data from these three groups were pooled for evaluation of effects on heart rate, blood pressure, and respiratory rate. For evaluation of the postanesthetic courses the five groups were treated separately.

The means and standard errors of the mean of the quantitative data are presented. Their statistical significance was determined by Student's t test. The significances of the incidences of various emergence phenomena were determined by the formula:

\[ Z = \frac{P_1 - P_2}{\sqrt{\frac{P_1(100 - P_1)}{n_1} + \frac{P_2(100 - P_2)}{n_2}}} \]

where \( P_1 \) and \( P_2 \) represent per cent incidence of a given phenomenon and \( n \) number of subjects, in the control and experimental groups, respectively.

**Results**

Some characteristics of the groups studied are compared in Table 1. Except for the somewhat more rapid return of consciousness in Group D (\( P < 0.05 \)), the five groups were similar. The circulatory changes are presented in tables 2 and 3.

The mean pulse rates (table 2) and the systolic and diastolic blood pressures (table 3) observed 20 to 40 min after atropine premedication with the patients supine were very similar in all groups. Placing the patients in the lithotomy position caused moderate, but statistically significant (\( P < 0.05 \)) increases in pulse rates (9 to 13 beats/min), systolic (6 to 13 torr) and diastolic (7 to 8 torr) blood pressures in all groups. The intravenous administration of 2.5 mg/kg ketamine caused further increases in heart rates. These increases were
TABLE 1. Characteristics of Patient Groups Receiving Ketamine

<table>
<thead>
<tr>
<th>Additional drugs</th>
<th>Group A (61 Patients)</th>
<th>Group B (50 Patients)</th>
<th>Group C (50 Patients)</th>
<th>Group D (61 Patients)</th>
<th>Group E (52 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Diazepam* (150 μg/kg)</td>
<td>Thiopental* (1.5 mg/kg)</td>
<td>Droperidol† (75 μg/kg)</td>
<td>Droperidol† (75 μg/kg)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>21.9 ± 0.71</td>
<td>24.6 ± 1.0</td>
<td>26.3 ± 1.0</td>
<td>24.6 ± 0.6</td>
<td>21.3 ± 0.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.8 ± 1.7</td>
<td>57.7 ± 2.4</td>
<td>63.7 ± 2.0</td>
<td>62.0 ± 1.6</td>
<td>62.9 ± 2.1</td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td>13.0 ± 0.6</td>
<td>14.7 ± 1.7</td>
<td>13.2 ± 1.0</td>
<td>12.9 ± 0.7</td>
<td>14.0 ± 1.1</td>
</tr>
<tr>
<td>Ketamine requirements (μg/kg/min)</td>
<td>267.3 ± 11.2</td>
<td>240.3 ± 17.8</td>
<td>256.0 ± 14.6</td>
<td>247.8 ± 13.5</td>
<td>240.1 ± 18.5</td>
</tr>
<tr>
<td>Time to recovery§ (min)</td>
<td>62.6 ± 3.8</td>
<td>69.3 ± 5.1</td>
<td>67.4 ± 5.4</td>
<td>52.0 ± 2.4</td>
<td>55.7 ± 3.0</td>
</tr>
</tbody>
</table>

* Administered iv at the end of operation.
† Administered iv 6 minutes before induction.
§ Mean ± SE.
§ From the last administration of ketamine.
¶ Significant, P < 0.05.

significant in Groups A, B, and C (P < 0.001),
premedicated with atropine alone, and also in
Group D (P < 0.05), which also received
droperidol before induction. In Group E,
which was given droperidol and fentanyl, ex-
cept at 2 min, pulse rates were lower than
pre-ketamine controls. At 2 min, systolic
and diastolic blood pressures were signifi-
cantly higher in all groups (P < 0.05), and they
remained above control throughout operation.
The administration of ketamine caused no clin-
ically significant change in respiratory rate.

The preanesthetic administration of dro-
peridol alone or droperidol with fentanyl did
not significantly decrease ketamine require-
ments (table 1), and actually facilitated re-
covery of consciousness. Statistically signifi-
cant shortening (P < 0.05) of the recovery
time, however, was observed only in subjects
who received droperidol alone.

Significant differences were observed in the
psychomotor and psychotomimetic effects
during and after recovery from ketamine anesthe-
sia (fig. 1). Compared with control values (Group A),
administration of droperidol (Group D) or droperidol and fentanyl (Group E)
before induction significantly reduced the
incidences of restlessness (P < 0.001), crying
(P < 0.05), and screaming (P < 0.01). The
postanesthetic administration of diazepam
(Group B) or thiopental (Group C) had no
significant effect on these emergence phe-
omena. The incidences of vomiting were
also lower in Groups D (P < 0.05) and E
than in Groups A, B, and C.

The observers noted (fig. 2) that at the
time of recovery somnolence was more fre-
quent (P < 0.01) in patients who received
droperidol (Group D) or droperidol and fen-
tanyl (Group E) than in the others. Before
discharge, however, only subjects of Group E
were more somnolent than those of the other
groups. The incidences of agitation (P <
0.01) and fright (P < 0.001), however, were
lower in patients who received droperidol or
droperidol and fentanyl than in the other
groups. By the time of discharge the inci-
dences of agitation and fright in the two
groups were not significantly different.

There was no significant difference among
the five groups in the percentages of patients
complaining of sleepiness or dizziness at the
time of recovery (fig. 3) or discharge. Hallu-
cinations, however, were less frequent (P <
0.05) in the droperidol (D) and droperidol-
plus-fentanyl (E) groups than in the control
(A) or diazepam (B) groups. The incidence
of hallucinations was higher than control in
the thiopental (C) group, but the difference
was not statistically significant. Most patients
who experienced hallucinations remembered
them at the time of discharge. It was not
feasible to do a psychological follow-up study
of these patients, but a week after operation,
at the postoperative visit, only one patient in
the control group (A) complained of her terrifying experience.

In no instance did the concomitant administration of the other drugs interfere with the scheduled discharge of the patients three hours after the last dose of ketamine. The differences between the preanesthetic and predischarge mean pulse rates, systolic and diastolic blood pressures, and respiratory rates, both supine and seated, were not significant.

**Discussion**

It is generally acknowledged that psychomotor and psychotomimetic effects limit the applicability of ketamine. Uncoordinated motor activity and crying and screaming during recovery create nursing problems and disturb other patients. The incidence of visual hallucinations in patients who seemed to be fully recovered had been reported to be 5 to 50 per cent.1-5 The unpleasant hallucinations may evoke hostile reactions in some patients, who complain bitterly of their terrifying experience and on occasion threaten to undertake legal action. For these reasons, in most institutions the use of ketamine is limited to anesthesia for selected procedures, such as neuroradiological tests6 and burn dressings7,8 in children.

Others have attempted to decrease tachycardia, hypertension, and the disturbing emergence phenomena by preanesthetic administration of pentobarbital,9 droperidol,10-12 diazepam,11,12 narcotic analgesics,9 scopolamine,2 promethazine,3 haloperidol,9 and various combinations of these agents.9 The results of these investigations are controversial. Dundee and his collaborators9 found that, of the various premedications investigated, droperidol with pheneridine and scopolamine with Pantopon were the most effective in reducing unwanted effects. In a more recent publication,14 they state that the combination of scopolamine and Pantopon is the most effective premedication for ketamine anesthesia. They found that 5 mg diazepam administered intravenously at

**Table 2. Changes in Pulse Rate**

<table>
<thead>
<tr>
<th>Time of Observation</th>
<th>Group A + Group B + Group C</th>
<th>Group D</th>
<th>Group E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before positioning</td>
<td>85.5 ± 1.2f</td>
<td>85.5 ± 1.5</td>
<td>85.5 ± 2.4</td>
</tr>
<tr>
<td>After positioning*</td>
<td>95.9 ± 1.4f</td>
<td>97.9 ± 1.9f</td>
<td>98.5 ± 2.5f</td>
</tr>
<tr>
<td>After ketamine 2 min</td>
<td>110.2 ± 1.4f</td>
<td>101.6 ± 1.5f</td>
<td>103.6 ± 2.7f</td>
</tr>
<tr>
<td>5 min</td>
<td>112.8 ± 1.5f</td>
<td>106.7 ± 1.5f</td>
<td>96.8 ± 2.6f</td>
</tr>
<tr>
<td>10 min</td>
<td>111.1 ± 1.5f</td>
<td>104.0 ± 2.2f</td>
<td>91.1 ± 3.7f</td>
</tr>
<tr>
<td>End of operation</td>
<td>107.7 ± 1.6f</td>
<td>100.9 ± 2.0</td>
<td>95.5 ± 3.3</td>
</tr>
</tbody>
</table>

* Subjects of Group D received 75 µg/kg droperidol iv and those of Group E, 75 µg/kg droperidol and 0.5 µg/kg fentanyl, 6 minutes before positioning.

† SE of the mean.

‡ Significant difference between before and after positioning values, P < 0.05.

§ Significant difference between pre- and post-ketamine values, P < 0.05.

**Table 3. Changes in Systolic and Diastolic Blood Pressures**

<table>
<thead>
<tr>
<th>Time of Observation</th>
<th>Group A + Group B + Group C</th>
<th>Group D</th>
<th>Group E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
</tr>
<tr>
<td>Before positioning</td>
<td>108.8 ± 0.9f</td>
<td>62.2 ± 0.7</td>
<td>107.6 ± 2.0</td>
</tr>
<tr>
<td>After positioning*</td>
<td>115.1 ± 1.2f</td>
<td>69.2 ± 0.9f</td>
<td>120.5 ± 2.3f</td>
</tr>
<tr>
<td>After ketamine 2 min</td>
<td>138.4 ± 1.6f</td>
<td>83.1 ± 1.1f</td>
<td>137.1 ± 2.0f</td>
</tr>
<tr>
<td>5 min</td>
<td>138.4 ± 1.6f</td>
<td>80.4 ± 1.2f</td>
<td>136.8 ± 2.0f</td>
</tr>
<tr>
<td>10 min</td>
<td>132.6 ± 1.7f</td>
<td>75.7 ± 1.2f</td>
<td>130.0 ± 3.0f</td>
</tr>
<tr>
<td>End of operation</td>
<td>126.0 ± 1.6f</td>
<td>74.1 ± 1.2f</td>
<td>125.8 ± 2.5</td>
</tr>
</tbody>
</table>

* Subjects of Group D received 75 µg/kg droperidol iv and those of Group E, 75 µg/kg droperidol and 0.5 µg/kg fentanyl, 6 minutes before positioning.

† SE of the mean.

‡ Significant difference between before and after positioning values, P < 0.05.

§ Significant difference between pre- and post-ketamine values, P < 0.05.
Fig. 1. Adverse effects during recovery. Drugs administered: Group A, ketamine only; Groups B and C, ketamine and 0.15 mg/kg diazepam or 1.5 mg/kg thiopental, respectively, at the end of operation; Groups D and E, 75 μg/kg droperidol or 75 μg/kg droperidol and 0.375 μg/kg fentanyl, respectively, 6 min before induction of anesthesia with ketamine. Statistically significant differences between control and experimental groups are indicated above the appropriate columns.

Fig. 2. Observations after recovery. Legend as in figure 1.
the end of operation decreased the incidence of unpleasant dreams. Diazepam, 10 or 30 mg administered intramuscularly before induction, had no effect on the circulatory side-effects, and the larger dose actually increased the incidence of unpleasant dreams. The beneficial effects of droperidol on the incidence and severity of emergence phenomena were confirmed by Sadove and his collaborators and by Crusius.

To eliminate some of the uncontrolled variables of earlier investigations, we studied a relatively large and homogeneous patient population. In the choice of drugs we were guided by the favorable results obtained by others with droperidol and diazepam. Thiorpental was selected because of its depressant effect on the sensory and motor cortex. A small dose of fentanyl was combined with droperidol in one group of patients because of the observation that narcotic analgesics prevent the transient psychomotor excitation occasionally seen after intravenous administration of droperidol.

Since the patients studied were outpatients, the doses of drugs were kept relatively small so that their after-effects would not interfere with early discharge from the hospital. For the same reason, droperidol, which has a long-lasting effect, was administered before induction of anesthesia, and the shorter-acting diazepam and the short-acting thiopental at the termination of surgery. Another reason for the preanesthetic administration of droperidol was to determine whether, because of its α-adrenergic-blocking activity, it had any preventive effect on ketamine-induced tachycardia and hypertension. These side-effects, attributed to catecholamine release, are preventable by ganglionic blocking agents. The unfavorable effect of diazepam on the psychotomimetic effects of ketamine observed by others with preanesthetic administration of diazepam also discouraged us from its use before induction.

Our findings confirm the previously-reported protective effect of droperidol against the disturbing psychomotor and psy-

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**Fig. 3.** Symptoms after recovery. Legend as in figure 1.
chotomimetic manifestations encountered during and after emergence from ketamine anesthesia (Figs. 1, 2 and 3). In contrast, under our experimental conditions, neither diazepam nor thiopental had any protective effect in this double-blind study. The incidence of hallucinations actually increased (P < 0.05) after thiopental. The combined use of droperidol and fentanyl did not seem to have any advantage over the use of droperidol alone in preventing emergence phenomena associated with ketamine anesthesia. The tachycardia (Table 2) and, to a lesser extent, the hypertension (Table 3) were partly antagonized by droperidol.

The high incidence of vomiting (Fig. 1), not usually encountered after ketamine anesthesia, can be attributed to the oxytocics used. Nausea and vomiting after the parenteral administration of ergot alkaloids occur in about 20 per cent of patients. The incidence of this complication was also reduced (P < 0.05) in the group that received droperidol.

We have no explanation for the more rapid recovery of consciousness in the group premedicated with droperidol. It is conceivable that droperidol, while inhibiting the excitatory effects (e.g., psychomotor and psychotomimetic activity) of ketamine in certain parts of the brain, antagonizes its depressant effects at other sites. However, the possibility that our method of evaluation of the patients' state of consciousness was not sufficiently accurate cannot be excluded.

The encouraging results in this study warrant further investigation of the use of droperidol for other types of both in- and outpatient. The finding that droperidol in the dose used did not delay recovery from anesthesia or the discharge of the patients because of its circulatory effects should be confirmed in patients of other age groups with various pathologic conditions. With the prevailing shortage of hospital beds, the extension of ambulatory or “day care” of surgical patients would have great socioeconomic significance.

References


