Fentanyl and Droperidol Effects on the Refractoriness of the Accessory Pathway in the Wolff-Parkinson-White Syndrome

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Using intraoperative electrophysiologic studies (ES), the authors analyzed the effects of various supplemental intravenous anesthetic agents on the antegrade and retrograde effective refractory period of accessory pathways (AERPAP and RERPAP) in the Wolff-Parkinson-White syndrome (WPWS), as well as their possible clinical implications. Serial evaluations were performed in 18 patients scheduled for surgical section of accessory pathways (AP) after anesthetic induction (thiopental + pancuronium + N₂O + fentanyl, 30 µg/kg), infusion of additional fentanyl (up to 50 µg/kg), diazepam (250 µg/kg), and successive doses of droperidol (200 µg/kg up to a total of 600 µg/kg). Neither the induction agents nor the addition of diazepam or fentanyl had a modifying effect on the refractory period of the accessory pathway, whereas droperidol significantly (P < 0.001) increased the AERPAP from 226 ± 8 to 356 ± 15 ms with a significant dose-effect correlation. The RERPAP also increased significantly (P < 0.001) from 220 ± 8 to 324 ± 9 ms. These results show that both the antegrade and retrograde refractory period of the AP increased with droperidol. Thus, droperidol may prevent the typical arrhythmias of the WPWS: rapid ventricular response due to antegrade conduction over the AP and reciprococal supraventricular tachycardia due to retrograde conduction over the AP. The authors’ clinical data support these findings. They concluded that there is a rational indication for the use of droperidol in the anesthetic management of the WPWS. (Key words: Anesthesia: cardiovascular. Anesthetics, intravenous: droperidol; fentanyl. Complications: arrhythmia. Heart: Arrhythmia; conduction; accessory pathway; Wolff-Parkinson-White syndrome.)

Sadowski and Moyers¹ established that successful anesthetic management of the Wolff-Parkinson-White syndrome (WPWS) and its variants depends on avoiding tachyarrhythmias by suppression of sympathetic stimulation and is predicated upon understanding the electrophysiologic and clinical manifestations. Other authors²⁻⁴ empirically recommend various anesthetic techniques based on hemodynamic stability and on the suppression of arrhythmias observed during their use. Electrophysiologic studies (ES) permit reproduction of the spontaneous life-threatening arrhythmias and assessment of their causative mechanisms and the conduction properties of the accessory pathway (AP). Furthermore, it is possible to perform serial pharmacologic tests with antiarrhythmic drugs and assess their effects on automaticity, refractoriness, and conduction.⁵ The existence of one or more pathways bypassing the atrioventricular node (AVN) is the basis for the appearance of arrhythmias in WPWS. The most frequent arrhythmias are reciprococ supraventricular tachycardia (RSVT) due to retrograde conduction over the AP, and atrial fibrillation (AF) which might induce a rapid ventricular response due to antegrade conduction over an AP with a short refractory period.⁶ Knowledge of the antegrade effective refractory period of the AP (AERPAP) is therefore of fundamental importance in recognizing high-risk patients.⁷ On the other hand, the initiation of a ventricuotrial reentry with RSVT implies a dissociation of the refractoriness of both pathways, so that the knowledge of the retrograde effective refractory period of the AP (RERPAP) will permit us to establish the maximum possible rate of reciprocal tachycardia.⁸ Ideally, pharmacologic treatment should consider the summation of effects exerted by the antiarrhythmic drug on each part of the circuit (atrium-AVN-ventricle-AP), and should attempt to eliminate refractory period differences between both systems when RSVT is the predominant phenomenon.

If ventricular arrhythmias represent the main risk, antegrade blockade of the AP would be desirable. This idealized approach, however, is actually more complex, due to the different actions of drugs on antegrade and retrograde conduction of the AP and their variable actions when used by oral or parenteral routes and at different dosages. These problems become partially superimposed when we use anesthetic agents that might modify the electrophysiologic properties of the circuit; there is limited experience with and little information about anesthetic effects on the AP.

We believe that the anesthetic management in cases of WPWS could be based on the knowledge of the effects of the anesthetic agents on the AP. Thus, the present study tests the possibility that some agents commonly used in anesthesia (namely droperidol and fentanyl), employed at several dosages, may modify the AERPAP and RERPAP and the clinical implications in the anesthetic management of these patients.

Materials and Methods

Eighteen patients (10 females and eight males) with Wolff-Parkinson-White syndrome and arrhythmias refractory to medical treatment were studied during surgery scheduled for section of the accessory pathway.
(AP). In all cases, an electrophysiologic study had been performed prior to surgery and the values of the AERPAP and RERPAP had been measured after confirmation of the presence of an AP. In 11 cases, the AERPAP was equivalent to the minimal RR’ in atrial fibrillation, and in the remaining seven cases it was measured by atrial pacing (see below). The intraoperative determination of both values was carried out using electrophysiologic studies (ES). Informed consent was obtained in each case.

Anesthetic Procedure

All preoperative antiarrhythmic drugs were discontinued in all 18 patients over 48 h prior to surgery, with the exception of amiodarone, which was discontinued at least two elimination half-lives in advance of surgery (more than 15 days). Every patient was premedicated 90 min before induction with morphine (0.1 mg/kg body weight, im). Once the patient was in the operating room, the ECG (leads I, II, and III), arterial blood pressure, central venous pressure (by internal jugular vein catheterization), esophageal and peripheral temperatures, and urine output were monitored.

Anesthesia was started with a fentanyl infusion at a rate of 150 μg/min and pancuronium (1 mg/min), under assisted ventilation via face mask with a 1:2 O₂ + N₂O mixture from the anesthetic machine. Thiopental, in divided doses up to a total of 3 mg/kg, was used for achieving unconsciousness. The arterial blood pressure and central venous pressure were maintained with an infusion of Ringer’s lactate solution. Endotracheal intubation was performed after administration of fentanyl (50 μg/kg) and pancuronium (100 μg/kg); after intubation, mechanical ventilation was maintained with a 1:2 O₂ + N₂O mixture and no more pancuronium was required until the institution of cardiopulmonary bypass. After this standard induction practice, only drugs for study purposes were used. After sternotomy and pericardiotomy, epicardial electrodes were placed and the first measurement of the AERPAP was performed. In nine cases no further fentanyl was used (Group 1) and in the other nine patients a further 20-μg/kg dose, at a rate of 150 μg/min, was given (Group 2). Diazepam (250 μg/kg) was administered over two minutes to three patients in each group. Droperidol was given in all 18 cases at a rate of 3 mg/min up to 200 μg/kg and two additional doses of 200 μg/kg each, at the same rate, were administered to six patients in each group, with a total dosage of 600 μg/kg. AERPAP measurements were performed five minutes after each dose. The RERPAP was measured only after the administration of the second and third doses of droperidol and after the epicardial charting had been performed and the AP located. After the last measurement, car-

diopulmonary bypass was started, endocardial mapping performed, and the surgical section of the AP carried out.

During the entire procedure, ventilation was controlled maintaining the PaCO₂ between 35 and 40 mmHg, and the serum pH and bicarbonate, sodium, and potassium levels were maintained constant.

Effective Refractory Period Measurements

Two bipolar epicardial electrodes were placed close to each other (less than 1 cm apart) on the apex of the left ventricle, and a similar electrode was placed on both atrial appendages. A further movable tripolar electrode (the exploring electrode) was successively placed on various epicardial areas of the ventricle, the atrium, and the His region. These electrodes were used both for recording the electrogram and for stimulation, which was carried out using an external stimulator designed and built in our hospital (LECPH 004/78) over a commuting switchbox. The signals derived from the electrodes were displayed on an oscilloscope and recorded (VR-8 Recorder, Electronics for Medicine Inc., White Plains, New York) and were filtered between 50–100 and 400 Hz (fig. 1). The recording included six conventional electrocardiographic leads and the electrograms at the above points.

In all cases, it was attempted to induce atrial fibrillation (AF) by means of high-frequency atrial stimulation on either atrium, and when this was achieved, the shortest interval between two successive preexcited beats (RR*) was considered to be the AERPAP (fig. 2). When AF was not achieved, atrial stimulation was used for calculation of this period, while ventricular stimulation was used in all cases for calculation of the RERPAP, as described previously, using programmed atrial or ventricular premature beats (A₂ or V₂), induced after eight spontaneous or conducted beats (A₁ or V₁).

The AERPAP was considered to be the longest A₁-A₂ interval near the AP which failed to conduct with preexcitation, and the RERPAP was the longest V₁-V₂ interval near the AP which failed to conduct over it.

Statistical Analysis

All values are expressed as means ± standard errors, in milliseconds (ms). Data were analyzed for statistical significance using Student’s paired t test, and comparisons were made between all the values. When sufficient data were available, Wilcoxon’s non-parametric analysis and the analysis of variance were applied between groups. The values achieved after the administration of droperidol were analyzed further with the Pearson correlation coefficient. P < 0.05 always was considered the significance level.
Results

Estimation of AERPAP

In two patients of Group 1 and one in Group 2, the values obtained were those achieved with extrastimulation; in the remainder, the AERPAP was the value of RR’ during AF. The measurement could not be carried out after the administration of fentanyl (30 μg/kg), droperidol (first dose), and droperidol (third dose), respectively, in three cases in Group 1 (see “n” in Table 1), nor after the infusion of additional fentanyl in one case in Group 2.

Group 1 (Fentanyl, 30 μg/kg)

The prior value of the AERPAP was 222 ± 9 ms, and the value after anesthetic induction (fentanyl, 30 μg/kg) was 237 ± 17 ms, a nonsignificant change. The administration of diazepam also failed to induce significant changes. However, the administration of droperidol increased the AERPAP to 292 ± 51 ms (P < 0.05), and highly significant increases (P < 0.001) were recorded after the second and third doses of droperidol, with a final AERPAP value of 348 ± 26 ms (Table 1).

Group 2 (Fentanyl, 50 μg/kg)

The prior value and that observed after anesthetic induction (fentanyl 30 μg/kg) was 231 ms. Neither additional fentanyl nor diazepam significantly modified this value. The first dose of droperidol, as in Group 1, increased the AERPAP to 273 ± 16 ms (P < 0.001). The second and third doses of droperidol given after 50 μg/kg fentanyl induced greater increases of the AERPAP (P < 0.001).

Groups 1 and 2 (Global)

According to the Wilcoxon test, droperidol in the three doses given induced significant increases of the AERPAP. For the full population studied, the prior value was 226 ± 8 ms, and the final value after a total dose of 600 μg/kg droperidol was 352 ± 15 ms (P < 0.05). The mean increase of the AERPAP was 41 ± 10, 59 ± 6, and 32 ± 4 ms after three successive doses of droperidol (Table 2). These increases show a highly significant correlation (r = 0.66, P < 0.001) with the doses used (Fig. 3), and the variance analysis also demonstrated statistical significance (F = 14.81, P < 0.001) for the difference between the prior value and the mean value for all doses of droperidol (312 ± 10 ms).

Estimation of RERPAP

We have no measurements of the RERPAP after anesthetic induction nor after the infusion of additional fentanyl, diazepam, or droperidol, 200 μg/kg. In the patients who were given 30 μg/kg fentanyl (Group 1) the prior value was 217 ± 9 ms, and after the second and third dose of droperidol highly, significant increases were achieved (P < 0.001), the final value being 324 ± 13 ms. In Group 2, the second and third doses of droperidol also increased the RERPAP value from 223 ± 13 ms (prior) to 324 ± 12 ms (final) (P < 0.001). Considered globally, these changes represent an increase from 220 ± 8 to 283 ± 18 ms, with good correlation (r = 0.79, P < 0.001) and statistical significance in the variance analysis (F = 28.57, P < 0.001).

Arrhythmias

In one case in Group 1, paroxysmal supraventricular tachycardia occurred immediately after sternotomy, prior to any manipulation of the heart by the surgeon. In the same patient and in two others (one in each
group), reciprocal supraventricular tachycardia with narrow QRS occurred during the placement of the epicardial electrodes (surgical manipulation). The arrhythmias were managed in three instances with direct 25 W/s electric shocks.

In another patient (Group 2), and prior to the administration of droperidol, there were two distinct bouts of atrial fibrillation with 170 beats/min ventricular response and severe hemodynamic consequences, which required cardioversion. A further episode of atrial fibrillation occurred immediately before the infusion of droperidol and remitted spontaneously when 100 μg/kg of the agent had been administered. The three episodes evidently were related to the surgical manipulation of the heart. No other arrhythmias occurred after the administration of droperidol.

Table 1. Values of AERPAP and RERPAP (in ms, Mean ± SE) after the Use of Different Supplemental Anesthetic Agents

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl (μg/kg)</th>
<th>Dizepam, 250 μg/kg</th>
<th>Droperidol (μg/kg)</th>
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<tbody>
<tr>
<td></td>
<td>Prior</td>
<td>50*</td>
<td>50</td>
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<tr>
<td>AERPAP</td>
<td></td>
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<tr>
<td>Group 1</td>
<td>222 ± 9</td>
<td>237 ± 17</td>
<td>216 ± 16</td>
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<tr>
<td>(n = 9)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
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<tr>
<td>AERPAP</td>
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<tr>
<td>Group 2</td>
<td>231 ± 13</td>
<td>231 ± 26</td>
<td>243 ± 29</td>
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<td>(n = 9)</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 9)‡</td>
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<tr>
<td>RERPAP</td>
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<tr>
<td>Group 1</td>
<td>217 ± 9</td>
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<td>(n = 9)</td>
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<td>(n = 9)</td>
<td>(n = 9)‡</td>
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<tr>
<td>RERPAP</td>
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</tr>
<tr>
<td>Group 2</td>
<td>223 ± 13</td>
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<td>(n = 9)</td>
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* Value after anesthetic induction.
† P < 0.05, ‡ P < 0.01, § P < 0.001 as compared with "prior value."

1 P < 0.05, ** P < 0.01, †† P < 0.001 as compared between columns.
The spontaneous arrhythmias recorded in the history and those induced during the electrophysiologic studies were reproduced without difficulty during the epicardial mapping. The induced atrial fibrillation was reverted with atrial extrastimulation, but in five cases cardioversion was required.

Discussion

The present work clearly shows that droperidol has an effect on the antegrade and retrograde conduction of the accessory pathway (AP), which is depressed by moderate doses (200 μg/kg) and much more when the dosage is increased to 600 μg/kg (fig. 3). Furthermore, because the RR' interval usually is shorter than the longest A₁-A₂, we should expect droperidol to induce actual increments of the AERPAP which are greater than those observed, together with a better dose-effect correlation, since in seven of our patients the previous AERPAP had been assessed by extrastimulation as well. Thus, the “prior AERPAP” values considered are probably greater than the actual ones. On the other hand, the RR' and A₁-A₂ intervals show a good correlation and both are used as a measure of the AERPAP; however, the measurement of RR' during atrial fibrillation is the better indicator of the possibility of ventricular fibrillation, and this is the reason why we have used this parameter.

We also have seen, using a procedure similar to the first one, that droperidol lengthens the RERPAP. The assessment of the RERPAP requires the accessory pathway to be precisely located and thus renders the exact measurement during the electrophysiologic study rather difficult. The “prior RERPAP” value therefore must be taken to be an approximation. This same difficulty prevents inratrope measurements until after epicardial mapping has established the location of the accessory pathway; as fentanyl and diazepam were administered prior to that time we were unable to assess their effect on retrograde conduction. Nevertheless the significant increase observed in the RERPAP upon increasing the droperidol dose from 400 to 600 μg/kg (table 2) causes us to suspect that the modification of the RERPAP only occurred when droperidol was given.

Prior to this study, several investigators had experimentally demonstrated that droperidol depresses conduction in the heart papillary muscle, and in the Purkinje fibres, and Bertolino et al. showed that it has antiarrhythmic properties. We now know that droperidol is able to: 1) depress the antegrade conduction of the accessory pathway and thus reduce the risk of rapid ventricular response, be it tachycardia or fibrillation; and 2) depress the retrograde conduction, thus tending to increase the cycle length of tachycardia or even to block ventriculoatrial conduction, thus disrupting the reentry mechanism. It is also possible that droperidol might narrow the atrial echo zone or dissociation margin between the normal conduction system and the accessory pathway, and in that case it would prevent the initiation of reciprocal tachycardia; indeed, the only tachycardias occurring in our series after the administration of droperidol were those induced by the electrophysiologic studies. Droperidol thus has a rational indication in these patients, and its beneficial actions on the accessory pathway do not interfere with inratrope electrophysiologic studies, a phenomenon which would seriously hamper this type of surgery. Furthermore, our clinical data in this study show a more stable rhythm after droperidol infusion (fig. 4), although greater postoperative central nervous system depression also was noted when 600 μg/kg were administered.

Conversely, we have not demonstrated any effect of fentanyl on the accessory pathway at dosages between 30 and 50 μg/kg, so that this agent would not be se-

| Table 2. Global Values of AERPAP and RERPAP (in ms, Mean ± SE) and Increments after Administration of Droperidol |
| --- | --- | --- | --- |
| | Prior | 200 μg/kg | 400 μg/kg | 600 μg/kg |
| AERPAP | 225 ± 8 (n = 18) | 282 ± 17* (n = 17) | 309 ± 13*+ (n = 11) | 352 ± 15* (n = 12) |
| ΔAERPAP | 41 ± 10 | 59 ± 6 | 32 ± 4 | |
| RERPAP | 220 ± 8 (n = 18) | 272 ± 13*+ (n = 9) | 324 ± 9* (n = 10) | |
| ΔRERPAP | 46 ± 9 | 53 ± 5 | | |

* P < 0.05 as compared with “prior value.”
† P < 0.05 as compared between columns.

Fig. 3. Variation of the values of AERPAP and RERPAP after successive doses of droperidol.
lectively indicated in these patients. However, fentanyl is associated with adequate hemodynamic stability,\textsuperscript{15,16} and might have bradycardia-inducing effects.\textsuperscript{17} Thus, the combination of droperidol and fentanyl could represent a good approach in the anesthetic management of these patients. Our previous experience supports this idea.\textsuperscript{18,8}

As an alternative to this technique, other authors\textsuperscript{1,4} propose the use of volatile agents such as halothane and enflurane. These agents induce adrenergic blockade,\textsuperscript{19} and Atlee \textit{et al.} have shown that halothane depresses conduction in the atrioventricular node, the His-Purkinje system, and the ventricular myocardium,\textsuperscript{20-22} and that enflurane prolongs the atrioventricular node conduction.\textsuperscript{23}

We have also had a good experience with these agents, even in special situations such as controlled arterial hypotension in the presence of WPWS,\textsuperscript{24} but we do not know if the effects observed by Atlee \textit{et al.} also affect the accessory pathway. We are at present studying these actions in our hospital, but we have not seen any important variations in the AERPAP or RERPAP in four patients managed with halothane–fentanyl. The use of these agents therefore is still based on empirical concepts.

The doses of thiopental and pancuronium that we have used in association with fentanyl–N\textsubscript{2}O had no apparent effects on the conduction of the accessory pathway. Pancuronium may increase the conduction of the atrioventricular node and cause tachycardia, but these actions do not seem to affect the accessory pathway,\textsuperscript{14} and therefore, variations in refractory periods of AP did not occur after anesthetic induction (table 1). In a similar manner, diazepam did not affect ERPAPs, although the low number of patients in whom it was used did not permit us to present any significant data. Finally, other variables necessarily introduced in our study, as temperature changes of the epicardium of the exposed heart and variations in the baseline conduction velocity of the different cardiac tissues by anesthesia also could affect the electrophysiologic parameters but our data suggest that these changes, if any, were slight and not significant.

Sadovsky and Moyers\textsuperscript{1} previously defined the objectives of the anesthetic management in these patients. Now, we conclude that effective prevention of arrhythmias may be attempted if we know the precise action of the anesthetic agents on the accessory pathway, and
that intraoperative electrophysiologic study is the means for such an assessment. Once the anesthesiologists know the precise effects of various anesthetic agents on the accessory pathway conduction, the anesthetic selection should be governed by data from preoperative electrophysiologic study of the patient. Thus, droperidol depresses the accessory pathway conduction with an apparent dose-effect correlation: its use would be indicated when the electrophysiologic study demonstrated a short AERPAP and there is a risk of rapid conduction over the accessory pathway. In these cases, adequate doses of droperidol might block the accessory pathway conduction. Fentanyl, thiopental, pancuronium, and N₂O do not affect conduction: they might be safe anesthetic agents in those patients with Wolff-Parkinson-White syndrome who present only a slight risk of severe arrhythmias. As Pry's-Roberts²⁵ has pointed out, investigations of anesthetic agents in humans using electrophysiologic studies are scarce, whereas the horizon of arrhythmia surgery is ever expanding.²⁶ This being so, further studies performed in these patients will be welcome.

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