The pharmacokinetics of methylprednisolone sodium succinate (MP) were studied in six neurosurgical patients under intensive treatment with large doses of MP, barbiturates, and mechanical hyperventilation. The study showed a remarkable level of enzyme induction within 24 hours after starting treatment, when the first blood samples were taken. The half-life \((t_\text{1/2})\) for MP during barbiturate and hyperventilation therapy was found to be reduced by a mean 55\% \((p < 0.01)\) in relation to the \(t_\text{1/2}\) of MP when administered alone. Studies on the day after termination of barbiturate intake indicated a tendency for an increase in the \(t_\text{1/2}\) of MP, but it was not significantly different from the pretermination assessment \((p > 0.05)\). On the basis of this study it is not possible to determine if the change in \(t_\text{1/2}\) alone is governed by enzyme induction or by a combination of this plus a change in the distribution and clearance of the steroid. The clinical implication of these findings is that patients who are undergoing steroid treatment and at the same time are sedated with barbiturates should have their MP dose increased in order to compensate for the marked reduction of \(t_\text{1/2}\) of MP.

**Key Words** - methylprednisolone • barbiturate • hyperventilation • enzyme production • sedation

Steroids are widely used in treating a variety of diseases, and can be given in low or high doses. The plasma half-life \((t_\text{1/2})\) of methylprednisolone (MP), when given in low doses, has been found to be 2\(\frac{1}{2}\) to 3\(\frac{1}{2}\) hours.\(^3\)\(^6\) Increasing the dose of prednisolone has been found to produce a prolongation of plasma \(t_\text{1/2}\), an increase in body distribution (distribution volume), and an increase in plasma clearance of prednisolone.\(^5\) Experiments have shown that low doses of barbiturates and phenytoin accelerate steroid metabolism by increasing hepatic microsomal enzyme activity,\(^1\)\(^6\) and consequently cause a reduction in the therapeutic effect of steroids.\(^1\)\(^4\)

This combined effect has not been tested with high doses of barbiturates. Therefore, in a prospective study, we have investigated the plasma \(t_\text{1/2}\) of MP in a group of neurosurgical patients who were treated with both MP and high doses of barbiturates during mechanical hyperventilation.

**Clinical Material and Methods**

**Patient Population**

Six patients aged 9 to 43 years (mean 22 years) were studied. Five patients (Cases 1, 2, 4, 5, and 6) had increased intracranial pressure (ICP) due to head injury and one (Case 3) had a brain tumor. None of the patients suffered from concurrent liver, kidney, or endocrine disease, and none had taken barbiturates previously.

**Therapy Protocol**

The patients with increased ICP were intubated with a nasoendotracheal tube connected to a respirator and then hyperventilated to a \(\text{PaCO}_2\) of 25 to 28 mm Hg, with \(\text{PaO}_2\) greater than 90 mm Hg. Pentobarbital (Mebumal) was given as a sedative in an initial dose of approximately 4 mg/kg body weight and a maintenance dose of 2 mg/kg/hr. Sedation continued for at least 2 days, and was extended depending on the patient's clinical condition. In addition, pancuronium bromide (Pavulon, 1 to 2 mg/hr) was given. The patients were cooled to a core temperature of 34° to 36°C, and an attempt was made to establish normohydration or slight dehydration. Methylprednisolone sodium succinate (MP) was given as an initial dose of 7 mg/kg body weight, followed by a maintenance dose of 40 mg/6 hrs intravenously in Cases 1, 2, 4, 5, and 6. The youngest patient (Case 3), who was aged 9 years, was given 20
Methylprednisolone half-life during barbiturate treatment

Fig. 1. Elimination curve for methylprednisolone in six patients after administration of barbiturate. Values represent means ± 1 standard deviation.

The samples were analyzed within 30 days from the date of collection. Determination of MP concentration in the serum was performed by a radioimmunoassay method carried out in the Upjohn Laboratory in London.2

Pharmacokinetic Evaluation
The MP elimination curve for the assessed 6-hour interval is recorded semilogarithmically. The inclination of the coefficient ($\beta$) in the terminal phase of elimination is determined. By extrapolation of the ordinate of the linear part of the terminal elimination curve, intercept B is found. This point shows the MP concentration following distribution time equal to zero. The $t_{1/2}$ is calculated by using the formula, $t_{1/2} = \frac{0.3010}{\beta}$, and the distribution volume for the $\beta$ phase ($V_{d\beta}$) using the formula, $V_{d\beta} = \text{dose}/\beta$. Plasma clearance (CL) is calculated using the formula,

$$CL = \frac{0.693 \times V_{d\beta}}{t_{1/2}}.$$

Statistical Method
The Mann-Whitney rank sum test for unmatched data was used for the statistical computations.

Results
The primary drug distribution phase was completed only after 1 to 2 hours (Fig. 1), so the serum concentration, determined 2 hours or more after MP intake, was used for the determination of $\beta$. Pharmacokinetic parameters for all patients are shown in Table 1. In four patients (Cases 1, 3, 4, and 6), MP elimination time was determined during simultaneous barbiturate treatment and again after barbiturates were discontinued. The elimination time was determined only during simultaneous barbiturate sedation in Cases 2 and 5.

The mean $t_{1/2}$ of MP for all six patients during the barbiturate course was 1.78 ± 0.73 hours (standard deviation), significantly lower ($p < 0.01$) than the $t_{1/2}$ for MP given without barbiturates as noted in the literature.3,6 The patients with both Series I and II measurements showed an MP $t_{1/2}$ of 1.35 ± 0.13 hours and 1.86 ± 0.59 hours, respectively. These were not significantly different ($p > 0.05$). The mean value of MP clearance in all six patients under barbiturate sedation was 30.4 ± 11.6 liters/hr. We did not find any significant difference in MP clearance in Cases 1, 3, 4, and 6 in Series I and II ($p > 0.05$). The mean values were 37.6 ± 6.6 liters/hr and 36.5 ± 12.2 liters/hr, respectively. Distribution volume for $\beta$ phase ($V_{d\beta}$) was 69.1 ± 15.2 liters in the six patients treated with pentobarbital, and for Cases 1, 3, 4, and 6, $V_{d\beta}$ was found to be lower in Series I than in Series II (72.8 ± 11.6 liters and 95.8 ± 40.3 liters, respectively). The mean value of plasma pentobarbital was 192 ± 63 $\mu$mol/liter immediately prior to termination of barbiturate intake.

mg/6 hrs intravenously. The doses were reduced after a week.

Sampling Protocol
In order to have comparable states of MP serum clearance, blood samples were taken from all six patients approximately 24 hours after simultaneous MP and barbiturate treatment (Series I), and from four patients (Cases 1, 3, 4, and 6) after barbiturate medication was discontinued, and plasma barbiturate levels were found to be zero (Series II). Blood samples were taken via a central venous catheter with the tip placed into the superior vena cava. The first sample (10 ml) was collected immediately prior to administration of MP. Further 10-ml samples were collected 1, 11, 2, 3, 4, 5, and 6 hours after administration of MP (see Fig. 1). Instead of taking a series of samples at two periods, which would have required 400 ml of blood in those patients in Series I and II, a second sample was collected only immediately prior to the next MP dose and was compared with the first sample in order to secure a steady-state level. The total sample volume for each patient therefore consisted of 200 ml of blood.

Serum Analysis
After each sample had been allowed to stand for 15 minutes at room temperature to form a soft clot, it was centrifuged for 15 minutes at 2000 G. The serum was then removed by pipette and deep-frozen to -20°C.
TABLE 1
Pharmacokinetic data calculated from MP serum concentrations in six patients following intravenous administration

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Test Series*</th>
<th>Intercept B (ng/ml)</th>
<th>Slope of β Curve</th>
<th>MP Half-Life (hrs)</th>
<th>Distribution Vol (liters) of β Phase</th>
<th>Clearance (liters/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>596</td>
<td>0.45</td>
<td>1.54</td>
<td>67.1</td>
<td>30.2</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>469</td>
<td>0.30</td>
<td>2.31</td>
<td>85.3</td>
<td>25.6</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>925</td>
<td>0.35</td>
<td>1.98</td>
<td>43.2</td>
<td>15.1</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>320</td>
<td>0.59</td>
<td>1.17</td>
<td>62.5</td>
<td>37.0</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>410</td>
<td>0.49</td>
<td>1.41</td>
<td>48.8</td>
<td>24.0</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>577</td>
<td>0.51</td>
<td>1.36</td>
<td>69.3</td>
<td>35.3</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>450</td>
<td>0.60</td>
<td>1.16</td>
<td>88.9</td>
<td>53.1</td>
</tr>
<tr>
<td></td>
<td>II</td>
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<td>3.00</td>
<td>80.0</td>
<td>16.8</td>
</tr>
<tr>
<td>5</td>
<td>I</td>
<td>433</td>
<td>0.52</td>
<td>1.33</td>
<td>92.4</td>
<td>48.1</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>250</td>
<td>0.27</td>
<td>2.57</td>
<td>160.0</td>
<td>43.1</td>
</tr>
</tbody>
</table>

* Series I: Blood samples for determination of methylprednisolone (MP) concentration taken during simultaneous barbiturate treatment.
Series II: Blood samples taken after barbiturate treatment.

Discussion

As this was purely a pharmacological study and the patients' condition was critical, the department's ordinary principles were followed for this group of patients. Therefore, the half-life of MP was determined for MP administered at six hourly intervals, and blood samples were collected after at least 24 hours of treatment, with the exception of Case 2, where collection was started after 16 hours. Thus, control of MP and of hyperventilation should be achieved, while it obviously was impossible to secure control of a possible enzyme disturbance. Pickup, et al., found the primary distribution phase completed after 30 minutes, whereas we first found it completed after approximately 2 hours. These findings cannot be explained without further research, but the reason might be that it is a matter of a three- or four-compartment model rather than a two-compartment model. This, however, cannot be determined on the basis of our results since there were too few concentration assays within the first 2 hours to allow for the construction of a precise distribution curve, and thus to determine the area under the curve. Instead of collecting two series of blood samples at six hourly intervals as a control, collection was limited to the last sample in the final interval only. This was because of the transfusion risk after sufficient blood was taken for analysis.

It would have been ideal if it had been possible to determine the half-life of MP in a group of conscious patients treated preoperatively with MP, and later to repeat the assessment on the same patients receiving postoperative respirator support under barbiturate sedation. This was not possible, but in one patient receiving only MP because surgery was cancelled we determined the half-life of MP and found it to be 3.9 hours, which is in accordance with the findings of Pickup, et al.

Cases 1, 3, 4, and 6 had a half-life of MP during barbiturate therapy of 1.35 ± 0.2 hours; that is, a mean decrease in the half-life of 55% (p < 0.01) compared with the normal MP elimination time. After termination of barbiturate intake the half-life was also found to be lower than usual but not significantly higher than in Series I.

The reason for this is probably that the numbers were too small and assessment was carried out immediately following termination of barbiturate intake, since enzyme induction caused by a barbiturate is unlikely to stop immediately the barbiturate intake is stopped. On the other hand, it seems that the effect of barbiturates is already apparent on MP half-life after 24 hours of administration and decreases shortly after withdrawal, with a tendency to a fall in MP clearance. The period of hyperventilation hardly affects the metabolic state, since the electrolyte and acid-base balance 1 to 2 days after stopping hyperventilation will be stable. The change in distribution volume of the β phase (Vdβ) contradicts the proposition that the change in fluid volume as a result of respirator treatment should influence the results. Because of the patients' clinical condition it was impossible, however, to obtain exactly the same interval between samples in Series I and II. For Cases 1, 3, and 6 the intervals between the Series I and II samples were 5 days, but for Case 4 the interval was 8 days. This extended treatment with barbiturates could possibly explain the lower half-life in Sample II in that patient, because of more pronounced enzyme induction. In Cases 2 and 5 it was only possible to collect Series I samples, and the half-life was somewhat higher in these two patients (Table 1). In Case 2, the cause might be attributed to a larger dose of MP in relation to body weight. Intercept B for this patient was considerably higher than that for the other patients, and furthermore this patient was only treated with barbiturate 16 hours before sampling. The patient in Case 5 had a lower body temperature (32°C) than the other five, and died. There is no other obvious explanation for the higher half-life in this patient, except that there might have been an analytical error.

From Table 1 it appears that there is no constant value in the distribution volume (Vdβ) in relation to the barbiturate treatment in Cases 1, 3, 4, and 6. Neither is the value of intercept B constant for Series I and II in
the same patients. As the MP dose is kept at a steady level, changes in the distribution volume ($V_{d0}$) occur which cannot readily be explained. In relation to these patients, it also appears that no constant connection between the change in clearance and change in $V_{d0}$ exists, whereas a decrease in $t_1$ is correlated to an increase in clearance. It can be concluded that the $t_1$ of MP will be 50% to 60% less with large doses of MP given simultaneously with high-dose barbiturates and mechanical hyperventilation. It is likely that an increase in clearance of MP is a contributing factor, but no definite conclusion can be reached with respect to the importance of possible changes in the distribution volume.

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References