Management of pemphigus
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Chapter IIIA

Pharmacokinetics of high-dose oral and intravenous dexamethasone

Abstract
Pharmacokinetics of intravenous and oral pulsed high-dose dexamethasone were studied in four patients with pemphigus vulgaris. Doses for dexamethasone were varied from 100 to 300 mg. Serum concentrations were measured by high-performance liquid chromatographic procedure with diode assay detection. Bioavailability was assessed by comparing the areas under the serum concentration-time curves following oral administration with those of intravenous administration. Mean bioavailability of high-dose oral dexamethasone was 63.4%. Side-effects were minor and were limited to temporary facial flushing both after oral and intravenous administration. Oral administration of dexamethasone in pemphigus patients showed to be more convenient and cost-reducing than administration by the intravenous route.
Introduction

Pulse therapy refers to discontinuous administration of very high doses corticosteroids. The choice of the corticosteroid and dosis of each pulse are not standardized, but usually are equal to 500-1000 mg methylprednisolone or 100-200 mg dexamethasone (1). The aim of this study is getting quicker and stronger efficacy and decreasing the need for long-term continuous corticosteroid use, and therefore reducing side-effects. Pulse therapy is reported to be successful in the treatment of many inflammatory or immunological diseases, i.e. cerebral edema, lupus nephritis, systemic vasculitis, severe asthma, multiple sclerosis, rheumatoid arthritis and pemphigus (1,2).

The intravenous route is often chosen for administration of high-dose pulsed corticosteroids rather than the oral route, despite the lack of evidence to support the presumed necessity of the intravenous route. Recent studies show equivalent therapeutic responses in patients with multiple sclerosis and rheumatoid arthritis after oral and intravenous administration of the same high dose of pulsed methylprednisolone (3-5).

In contrast to methylprednisolone, no efforts have been made to elucidate the pharmacokinetics of high-dose dexamethasone, despite its negligible sodium-retaining properties, low equipotent volume, and nil presystemic metabolism. It is conceivable, although not convincingly proven, that dexamethasone is less likely to cause serious cardiac dysrhythmias than methylprednisolone (6).

This study was undertaken to elucidate the pharmacokinetics of intravenous and oral high-dose pulses dexamethasone, and estimate the adequate dosis for the oral route.

Materials and Methods

Subjects

Approval for this study was obtained from the medical-ethical committee of the hospital. Informed consent was obtained from each patient. The patients were treated with prednisolone maintenance therapy in addition to dexamethasone pulse therapy every month in courses of three consecutive days.

Four pemphigus vulgaris patients were enrolled in this study. The patients comprised three males with an average age of 35.3 years (range 28-46), and mean weight of 77.5 kg.
Pharmacokinetics of high-dose dexamethasone

(range 74-83), and a 51 year old female with a body-weight of 92.4 kg. All patients were on daily doses of oral prednisolone 10-60 mg, ranitidine 150 mg, and a combination of etidronate and calcium carbonate (Didrokit®). One patient was also taking azathioprine 150 mg daily. Two patients suffered from a steroid-induced diabetes, requiring either insulin or tolbutamide. There were no further concomitant diseases in the medical histories. Pulse therapy was performed clinically. Every patient was given a complete medical history and physical examination. Prior and after pulse therapy safety parameters in blood (hemoglobin concentration, hematocrit, leucocytes (differentiation), trombocytes, eosinophils, liver function, kidney function, glucose) and urine (sediment, reduction) were measured. During pulse therapy every hour blood pressure and heart rate were monitored as well as blood glucose levels in the diabetic patients.

Drug administration

Patients were given 100, 200 and 300 mg dexamethasone by oral and intravenous route according to Table 1. There was no sequence of administration. The period in between each dexamethasone dose was at least 24 hours.

For intravenous administration the water-soluble ester dexamethasone phosphate was used, since dexamethasone has a low water solubility. For oral administration dexamethasone was used.

- Therapy 1: Intravenous administration over one hour of 200 mg dexamethasone-phosphate.
- Therapy 2: Intravenous administration over one hour of 100 mg dexamethasone-phosphate.
- Therapy 3: Oral administration of 200 mg dexamethasone; two gelatin capsules containing 100 mg of dexamethasone.
- Therapy 4: Oral administration of 300 mg dexamethasone; three gelatin capsules containing 100 mg of dexamethasone.

The high-dose dexamethasone capsules were made by the hospital pharmacist, since the highest dose in tablets available in the Netherlands is only 6 mg. The patients were not fastened prior to the oral dose. The capsules were swallowed with a glass of water.
Table 1: Treatment schedule

<table>
<thead>
<tr>
<th>Therapy 1; 200 mg dexamethasone i.v.</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Therapy 2; 100 mg dexamethasone i.v.</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Therapy 3; 200 mg dexamethasone per os</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>X</td>
</tr>
<tr>
<td>Therapy 4; 300 mg dexamethasone per os</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Legend: 'X' represents single administration on a separate occasion, i.v.=intravenous, dexa=dexamethasone

Sample collection

Blood samples were drawn in 5 ml non-heparinised tubes during the first or the second day of a pulse course. Blood samples were drawn between 0 and 15 hours after oral and intravenous administration (Fig. 1). The samples were centrifuged and the serum stored at -20 °C until further analysis. The blood samples were collected within a period of six months.

Pharmacokinetic analysis

Serum samples were analyzed for dexamethasone concentrations by a selective high-performance liquid chromatography (HPLC) procedure. Betamethasone (1 mg/L) was used as internal standard.

The chromatographic system incorporated an analytical column (Chromsphere 5C18, 250*4.6 mm), a guard column (Chrompack R.P., 10*2.1 mm), an autosampler (Merck-Hitachi, model AS-2000), a high-pressure pump (Separations, model 300) and a diode array detector (Gynkotek) at 244 nm with computer software to achieve data handling and peak integration. As mobile phase a mixture of phosphate buffer (10 mM, pH 6.9) and tetrahydrofuran (75:25) was used at a flow rate of 1.25 ml/min. One ml of serum was extracted with 6 ml diethylether after addition of 250 µl of internal standard. After shaking for 15 minutes and centrifugation for 5 minutes the water layer was frozen by -40 °C and the organic layer was transferred into a clean test tube, and evaporated to dryness under nitrogen. The residue was reconstituted in the mobile phase (200 µL) and 40 µL of aliquot was injected into the HPLC. Serum concentrations of dexamethasone were calculated by means of the ratio of its peak height to the peak height of the internal standard. The low level of quantitation was 25 µg/L. CV’s (Coefficient of Variation) for
Pharmacokinetics of high-dose dexamethasone

30.0 mg and 100.0 mg dexamethasone per litre of human serum was 1.2 % and 1.3 % interday, 2.0 % and 2.9 % intraday respectively.

For pharmacokinetic analysis the computer program MW/PHARM was used (7). This program fits the optimal compartment model, with the least square method, and calculates pharmacokinetic parameters.

For all administrations the time course of serum dexamethasone concentrations were characterized by a peak concentration ($C_{\text{max}}$), time of peak concentration ($t_{\text{max}}$), area under the serum-concentration time curve (AUC), and the half life ($t_{\frac{1}{2}}$). Bioavailability ($f$) of the orally administered dexamethasone dose was estimated according to equation:

$$f = \frac{AUC_{\text{oral}} \times \text{dose}_{\text{i.v.}}}{AUC_{\text{i.v.}} \times \text{dose}_{\text{oral}}}$$

$AUC_{\text{oral}}$ and $AUC_{\text{i.v.}}$ are the area under the serum dexamethasone concentration time curve for the oral and i.v. doses, respectively.

In vitro dissolution of the capsules was tested following the standard method described in the European Pharmacopoeia (8). The capsules were compared to a standard (known quantity substance). After one hour the maximum dissolution was achieved.

Results

During therapy no serious adverse effects occurred. In about 60 percent of the cases minor side-effects of facial flushing and sleep disturbance occurred during pulse therapy. There was no difference between intravenous and oral administration in regard to these minor side effects. Dexamethasone was not detectable 24 hours after intravenous or oral administration in any of the patients. Therapeutic effects were not relevant in this study, since the follow-up after each pulse was only 24 hours, too short to expect any effect on the skin lesions.

Figure I shows mean concentration-time curves for each administration. Here it is demonstrated that the ‘area under the curve’ after 300 mg orally approximates the same pharmacokinetic parameter after 200 mg i.v. better than after administration of 200 mg...
p.o. The dexamethasone peak concentration after 300 mg oral dexamethasone ($C_{\text{max}}$) was 72.3% of the intravenous level at 200 mg i.v.

Figure I: Mean dexamethasone concentrations (mg/L) in all patients as a function of time (hours)

All serum concentration time data, including mean and standard deviation (S.D.), during a total of 14 cycles of treatment are summarized in table II. This table demonstrates for patient B and C the intraindividual differences in time until peak concentration ($T_{\text{max}}$), and peak concentration ($C_{\text{max}}$). Data for all doses were best described by a two compartment pharmacokinetic model using the computer program MW / PHARM.

Mean peak concentration was 4.45 mg/l after administration of 200 mg intravenously. The infusion time was one hour. The same dosage per os led to a mean peak concentration of 1.98 mg/l after 2.21 hours, and the mean bioavailability was 64.5%. In terms of area under curve this means that 200 mg dexamethasone per os is equivalent to 129 mg dexamethasone i.v. When 300 mg dexamethasone per os was given, mean bioavailability remained constant (61.3%), but mean peak concentration was at considerably higher level of 3.22 mg/l. Mean time to maximum concentration was 3.17 hours. Area under curve after 300 mg dexamethasone per os is equivalent to 184 mg
dexamethasone i.v. Efforts to assess the statistical significance level of the differences observed in this study were not made because of the low number of patients.

Table II: Pharmacokinetic parameters of dexamethasone after high-dose oral or intravenous therapy.

<table>
<thead>
<tr>
<th>Patient</th>
<th></th>
<th>A</th>
<th>B1</th>
<th>B2</th>
<th>C1</th>
<th>C2</th>
<th>D</th>
<th>mean</th>
<th>s.d.</th>
</tr>
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<td><strong>therapy 1: 200 mg dexamethasone i.v.</strong></td>
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<td></td>
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<tr>
<td>AUC (h mg/l)</td>
<td>16.62</td>
<td>17.36</td>
<td>10.11</td>
<td>15.84</td>
<td>14.98</td>
<td>3.31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/l)</td>
<td>4.74</td>
<td>4.44</td>
<td>3.81</td>
<td>4.81</td>
<td>4.45</td>
<td>0.46</td>
<td></td>
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<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>2.51</td>
<td>2.15</td>
<td>0.66</td>
<td>3.61</td>
<td>2.23</td>
<td>1.22</td>
<td></td>
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<tr>
<td><strong>therapy 2: 100 mg dexamethasone i.v.</strong></td>
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<tr>
<td>AUC (h mg/l)</td>
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<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/l)</td>
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<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>1.01</td>
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<tr>
<td>AUC (h mg/l)</td>
<td>11.04</td>
<td>11.09</td>
<td>9.34</td>
<td>5.78</td>
<td>7.51</td>
<td>11.44</td>
<td>9.36</td>
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<tr>
<td>Bioavailability (%)</td>
<td>66</td>
<td>64</td>
<td>54</td>
<td>57</td>
<td>74</td>
<td>72</td>
<td>64.5</td>
<td>7.94</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/l)</td>
<td>2.05</td>
<td>1.90</td>
<td>1.85</td>
<td>1.66</td>
<td>1.11</td>
<td>3.28</td>
<td>1.98</td>
<td>0.72</td>
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<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2.50</td>
<td>3.00</td>
<td>1.25</td>
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<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>2.66</td>
<td>1.62</td>
<td>2.06</td>
<td>3.09</td>
<td>1.09</td>
<td>0.78</td>
<td>1.88</td>
<td>0.90</td>
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<td><strong>therapy 4: 300 mg dexamethasone per os</strong></td>
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<tr>
<td>AUC (h mg/l)</td>
<td>14.69</td>
<td>15.77</td>
<td></td>
<td></td>
<td>15.23</td>
<td>15.23</td>
<td>0.54</td>
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<tr>
<td>Bioavailability (%)</td>
<td>59</td>
<td>61</td>
<td></td>
<td></td>
<td>64</td>
<td>61.3</td>
<td>2.52</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/l)</td>
<td>3.01</td>
<td>3.16</td>
<td></td>
<td></td>
<td>3.50</td>
<td>3.22</td>
<td>0.25</td>
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<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>3.50</td>
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<td></td>
<td></td>
<td>2.50</td>
<td>3.17</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>1.97</td>
<td>2.17</td>
<td></td>
<td></td>
<td>1.72</td>
<td>1.95</td>
<td>0.23</td>
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</tbody>
</table>
Discussion

In this study mean bioavailability of oral high-dose dexamethasone was 63.4% (range 54-74%). Bioavailability levels reported in the literature for oral low-dose dexamethasone show wide variation (53-112%) (6).

In terms of AUC, oral 300 mg dexamethasone was calculated to be equivalent to 184 mg intravenous dexamethasone. Given the relative potency of methylprednisone to dexamethasone of 4:0.75, the often clinically used intravenous dose of 1000 mg methylprednisone is equivalent to 187.5 mg dexamethasone intravenously. Since it is still unknown whether the effects of pulse therapy are due to the peak concentration ($C_{\text{max}}$) or the time-dose effect (AUC), 300 mg dexamethasone is the preferable dose to be used in oral pulse therapy.

No major side-effects of high-dose dexamethasone pulses were observed during this study. Furthermore, dexamethasone is cleared from the circulation within 24 hours, so that repetitive pulses on subsequent days do not lead to accumulation in the blood. Since dexamethasone has no known presystemic metabolism (9) there is no reason to worry for first-pass effects or liver damage after high-dose oral boluses. All our patients also received daily treatment with prednisolone and ranitidine. The possible influence of low dose prednisolone treatment (not detected by HPLC in this study) on high dose dexamethasone kinetics might be negligible. There is also no documented pharmacokinetic interaction between ranitidine and dexamethasone.

The clinical effects were not studied here. Recent studies however, showed no differences in efficacy and safety of oral versus i.v. pulsed high-dose corticosteroids in patients with multiple sclerosis and rheumatoid arthritis (3-5).

In conclusion, the bioavailability of high-dose dexamethasone is 63.4 percent after oral administration. Administration of 200 i.v. or 300 p.o. dexamethasone appears to be safe. This study suggests that changing the clinical use of intravenous pulses of 200 mg dexamethasone or 1000 mg methylprednisolone into oral pulses with 300 mg dexamethasone would avoid an invasive technique (vena puncture), reduces patients inconvenience, and increases cost-effectiveness, since oral intake requires less demands on medical staff and hospital room than intravenous delivery.
Acknowledgments

We gratefully acknowledge Jan van deer Molen, Department of Clinical Chemistry, for his skillful technical assistance. This study was financially supported by the Board of Directors of the Groningen University Hospital.

References

Chapter III-B

Dexamethasone pharmacokinetics after high-dose oral therapy for pemphigus

To the Editor

High-dose glucocorticoid pulse therapy aims at periodically strong immunosupression, and may reduce the daily maintenance dose of glucocorticoids thus limiting the hazards of continuous long-term steroid intake (1). The high-dose glucocorticoids are administered every month on three consecutive days. Type of glucocorticoid and dose per pulse is not standardised but usually 500-1000 mg methylprednisolone per pulse, or 100-200 mg dexamethasone per pulse is administered (2). Pulse therapy is mostly given intravenously rather than orally, without evidence to support the necessity of the intravenous route. Oral therapy is preferable, avoiding vena-punctures, decreasing costs, and for patient-convenience.

Recently, the bioavailability of oral high-dose dexamethasone (100 mg capsules) of 63.4% was determined (3). In this study, the pharmacokinetics of a new dexamethasone formulation was studied, namely 50 mg tablets for oral use in pulse doses of 300 mg.
Methods

Four patients with pemphigus vulgaris currently on pulse therapy were enrolled in this study. In each patient the intravenous pulse therapy was replaced by tablets for one pulse cycle. Time in between consecutive pulses was more than 24 hours. Tablets containing 50 mg dexamethasone were produced in our hospital pharmacy. The dexamethasone (Eur. Pharm) was hydrophilised with methylcellulose 15 MPA-s (Eur. Pharm). The tablets were prepared by direct compression using cellulose mycrocrystalline (Eur. Pharm, Avicel pH101) and magnesium stearate (Eur. Pharm).

Serum samples were drawn after intravenous and oral pulse administration and analyzed by a validated suitable selective high performance liquid chromatography procedure. The same analytical procedure and extraction was used as in the previous study (see methods chapter IIIA).
Results

Figure I shows the mean serum concentration-time curve for both oral and intravenous administration of dexamethasone. The serum concentration-time curves corresponding to these administrations were best described by a tri-exponential equation. Mean bioavailability of the tablets was 55.8% (range 43-65%). Mean peak concentration after 200 mg dexamethasone iv. was 5040 µg/L, after 300 mg dexamethasone per os 2580 µg/L. Mean time to peak concentration is 2.25 hours for oral administration.

Figure I. Mean dexamethasone serum concentrations (mg/L) in all patients as a function of time (hours)
Discussion

When tablets of 50 mg were used mean dexamethasone peak concentration (C\text{max}) was 52% (range 37-66%) of the intravenous level at 200 mg i.v., which is lower than after administration of the capsules (mean 72.3%; range: 67-79%) (see chapter IIIA). The dose of 358 mg dexamethasone per os is equivalent to 200 mg dexamethasone iv. Bioavailability does not differ significantly when 50 mg tablets (58.8%) or 100 mg capsules (63.4%) are used.

Since it is unknown whether the effects of pulse therapy are due to C\text{max} or AUC and the bioavailability (AUC) of the tablets was comparable to capsules we concluded that 300 mg oral dexamethasone in 50 mg tablets can be used as oral pulse therapy. Tablets are preferable instead of capsules, for better \textit{in vitro} control of content uniformity and better taste correction. Intake of tablets is more convenient than of capsules for the patient.

The new dexamethasone tablets have reliable pharmacological and technical characteristics, and appear to be safe. They can be safely used for high-dose pulse therapy, and are suitable for use in the planned clinical trials, in which the therapeutic effect of oral high-dose dexamethasone pulse therapy is evaluated.

References