PART XI

Symposium  ON CORTICOSTEROID DOSAGE IN
RENAL TRANSPLANTATION

Chairman:  M G McGeown
CORTICOSTEROID DOSAGE IN RENAL TRANSPLANTATION

CORTICOSTEROID THERAPY FOR RENAL TRANSPLANTATION

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Corticosteroid, in the form of ACTH, was used for human renal transplantation by Kuss, Legrain and Mathe [1] as long ago as 1951. Hume, Merrill and Miller [2] also used ACTH in 1952. Although one graft functioned for a few weeks all soon failed.

Corticosteroid was used in combination with azathioprine by Starzl, Hume, Murray and Woodruff, all in 1962. In the same year Goodwin [3] reported that very large doses of corticosteroid reversed rejection in a graft (mother to child) being treated with nitrogen mustard and cytoxan.

The way in which corticosteroids exert an immunosuppressive effect on the transplant situation is still not understood. They may suppress inflammation occurring in the transplanted organ as part of the rejection response, or they may intervene at the point of induction of the immune response. Moreover, there is no general agreement as to how they should be used. Corticosteroids are relatively ineffective immunosuppression agents when given alone and are always given combined with a cytotoxic drug, usually azathioprine. Other drugs may be added.

In this symposium we will attempt to answer some questions pertinent to the use of corticosteroid for renal transplantation.

Since 1962 corticosteroid has been used along with azathioprine for what may be termed base-line immunosuppression, and also given in large, sometimes very large, doses for the treatment of rejection. The greatest variation seems to be in its use as a base-line immunosuppressive drug.

Let us consider factors which may be of importance in the use of steroid, including the route of administration, the choice of drug, absorption including effect of food and other drugs, the time at which it is given, and the rate at which dosage is reduced.
Route

The first dose of steroid is usually given intravenously during the transplant operation. After the first 24 hours in most transplant units it is given orally. Woods et al [4] recommend intravenous steroid therapy for two or three weeks for diabetic recipients, but continued intravenous administration appears to be exceptional.

Choice of steroid

ACTH does not appear to have been used after the very early transplants. Glucocorticoids are more suitable because they can be given orally as well as parenterally, the dose is more easily adjusted and response does not depend on adrenal responsiveness. Moreover, they produce less hypertension, acne and pigmentation than ACTH. The glucocorticoids used are prednisone, prednisolone and methylprednisolone. Prednisonone is converted into prednisolone in the liver, and provided liver function is adequate it would appear that either drug can be used. Prednisone appears to be used in most centres in America, while some British and European centres use prednisolone. Both drugs are rapidly absorbed after oral administration, the peak plasma level occurring within one to three hours [5]. On average the bioavailability of prednisolone after oral ingestion of prednisone is approximately 80% of that after prednisolone, but there appears to be wide individual variation in the ability to convert prednisone to prednisolone [6]. As the plasma level appears to be more predictable after administration of prednisolone there may be a slight advantage in the use of prednisolone.

Absorption and bio-availability

Prednisolone has been given as enteric-coated tablets in the hope of reducing the risk of peptic ulceration, but it has been reported that the absorption of prednisolone from these tablets is very variable. Unabsorbed tablets have been found in the bowel many hours after ingestion and it is probably best to avoid using enteric-coated tablets [7]. Absorption is delayed by food ingested at the same time. Even in normal subjects there are unexplained differences in the rate of absorption [6]. However, the therapeutic effect persists longer than the half life in blood would suggest.

Prednisolone once absorbed or formed from prednisone by the liver, is bound by plasma albumen and the free (i.e. active) form is increased by hypoalbuminæmia [5].

Effects of other drugs

Drugs which cause induction of hepatic microsomal enzymes, such as barbiturates, phenytoin and rifampicin, shorten the half life of prednisolone, thereby reducing its therapeutic effect [5].

In some parts of the world anti-tuberculosis drugs are given routinely following transplantation. Anti-convulsant drugs given prior to transplantation may be continued afterwards. In both circumstances the therapeutic effect of prednisolone
will be reduced. Information is lacking about the effects of other drugs, including azathioprine, on the absorption and bio-availability of prednisolone.

Timing

Normal cortisol secretion is highest in the morning and lowest in the evening. It would seem logical to try to reproduce this natural diurnal rhythm when using cortisol as a therapeutic agent but evidence on this point is difficult to find.

The half life of injected cortisol is in the range of 80–115 minutes, prednisone 60 minutes, prednisolone 115–252 minutes (but prednisone is converted into prednisolone) and dexamethasone 110–210 minutes, methylprednisolone 78–188 minutes. Prednisolone and dexamethasone have comparable circulating half lives but marked difference in potency. The duration of ACTH suppression exceeds the half life by more than the 5-fold factor that would be expected if the duration of effect was a function of the circulating level of the steroid. The duration of the action of a glucocorticoid therefore does not appear to be dependent on its presence in the circulation and in fact clinical data (e.g. relief of pain in rheumatoid arthritis) suggests it is much longer.

A single daily dose of steroid given in the morning appears to be as effective as divided doses. The manifestations of Cushing’s syndrome, with the possible exception of peptic ulcer, are not prevented or reduced by giving a single daily dose. However, suppression of hypothalamic-pituitary-adrenocortical function is less with a single morning dose than with a single evening dose or with the dose divided over the day [8,9].

A recent survey of British transplant units showed that the majority gave the dose of steroid divided over the day, while some gave the total dose in the evening, and only two gave a single morning dose [10].

Less adrenopituitary suppression results when the corticosteroid is administered on alternate days even if the total dose remains the same [11]. The basis for the use of alternate day corticosteroid therapy is the hypothesis that the anti-inflammatory effects persist longer than the undesirable metabolic effects. The interval between doses is empirical and 48 hours was chosen because clinical effect was apparent at that time but not after 72 hours. Many have reported the efficacy of alternate day steroids in preventing rejection and commented upon the reduction in side effects. It is not clear how soon after transplantation it is safe to change to alternate day therapy, or exactly how the change-over should be managed [12]. There is some risk of rejection following the change-over but in our own experience this appears to be slight.

It has been suggested that the dose given for alternate day therapy may need to be more than double the daily dose to obtain equivalent immunosuppression, but the toxicity remains much less [13]. However, other reports suggest that it is sufficient to give the same total 48 hour dose [14]. Alternate day steroid improves growth of children following transplantation, and as children frequently become Cushingoid it is advantageous to make the change-over within a few months after operation [15]. Moreover, the conversion may be safer before there has been prolonged adrenopituitary suppression.
Dosage

There is a very wide variation in the dosage of corticosteroids used in the early post-transplant period (Table I). The doses shown in the table are minimal doses and patients who develop rejection receive much more.

Our own corticosteroid regimen is the lowest dosage shown on this table.

TABLE I. Dosage of corticosteroid used for renal transplantation

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGeown et al [16]</td>
<td>First 24 hours 800mg hydrocortisone i.v.</td>
</tr>
<tr>
<td></td>
<td>Second 24 hours onwards 20mg prednisolone oral.</td>
</tr>
<tr>
<td>Simmonds et al [17]</td>
<td>20mg methylprednisolone/kg/day for 3 days,</td>
</tr>
<tr>
<td></td>
<td>2mg/kg/day reducing to 0.5mg/kg/day at 1 month.</td>
</tr>
<tr>
<td>Butt et al [18]</td>
<td>120mg prednisone reducing to 30mg/day at 1 month.</td>
</tr>
<tr>
<td>Traeger et al [19]</td>
<td>1mg/kg/day tapered.</td>
</tr>
<tr>
<td>Morris et al [20]</td>
<td>100mg/day reduced by 5mg every 5 days to 20mg.</td>
</tr>
<tr>
<td>Chatterjee [21]</td>
<td>2mg/kg day −1, 0, 1; 1.8mg/kg day 2–4;</td>
</tr>
<tr>
<td></td>
<td>1.6mg/kg day 5–7; diminishing in 3 day steps to 0.6mg/kg at day 21, then 0.5mg/kg/day for 3 weeks, 0.4mg/kg/day for 6 weeks.</td>
</tr>
</tbody>
</table>

Rate of reduction of dose

The lack of uniformity both in the initial dose of steroid and in the rate at which the dose is reduced is illustrated in Figure 1. Some centres use high initial doses reducing to a fairly low level at about one month. Others commence with a somewhat lower dose but reduce much more slowly to a similar dose. We gave 20mg daily from the day following transplantation, which seems to be the lowest dosage in use. Almost all centres eventually reduce the dose of prednisone or prednisolone to 10mg daily, or sometimes to 20mg on alternate days. The reduction is carried out gradually but opinions vary about how long should be taken to reach the long-term maintenance dose. There is no clear evidence as to how rapidly the dose of steroid can be reduced with safety for the continued function of the graft. At least one centre in the United Kingdom reduces the dose to 10mg daily at 3 months, but most wait for 6 months or longer.

The cumulative survival rate for all first cadaver grafts carried out in Belfast 1968 to 1979 is shown in Figure 2. The dose of steroid used was 20mg per day as shown in Figure 1. The lower line excludes death with a functioning graft. The cumulative graft survival at 2 years is 76%. Moreover, the low dose of steroid is
Figure 1. Rate of reduction of dose of steroid

McGeown et al [16]
Simmonds et al [17]
Butt et al [18]
Morris et al [20]
BELFAST - 1ST CAD. GRAFTS

Figure 2. Cumulative survival rate of first cadaver grafts carried out in Belfast 1968 to 1979.
- includes death with functioning graft
- excludes death with functioning graft
--- mean graft survival UK centres

associated with a very low incidence of the side effects well known to complicate high dosage of steroids [22].

Since it is clear that as little as 20mg of prednisolone from the day following transplant is sufficient to provide a good graft survival rate, it is reasonable to ask whether transplantation can be carried out without the use of steroid at all.

Professor Crosnier has information about this point and I will ask him to give his paper now.

The use of corticosteroid for anti-rejection therapy has not yet been mentioned and Dr Brynger will deal with this aspect later.

Acknowledgments

I acknowledge generous financial support from the Northern Ireland Kidney Research Fund.

I wish to thank UK Transplant for Figure 2.
ARE THERE NON-STEROID-DEPENDENT REJECTION EPISODES?

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Introduction

Two different mechanisms leading to graft rejection are generally described. The first involves the presence of antibodies directed against the graft antigens and is responsible for vascular lesions. The second, of cellular origin, results in cellular infiltration of the kidney and