THE TIMING OF IMMUNOSUPPRESSIVE THERAPY AND SUPPRESSION OF THE IMMUNE RESPONSE

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Introduction

At least some of the immunological processes involved in allograft rejection vary on a circadian basis, i.e. around the 24 hours. Our studies in oxazolone sensitised rats demonstrated that the time of day or night of further encounters with the antigen influences the magnitude of the immune response that results [1,2]. This response is of the delayed hypersensitivity cell-mediated type, with maximum responses at one time being many times greater than the minimum responses at another. In man, studied in healthy students already sensitised to tuberculin, the response to subsequent exposure was 2½ times greater at 0700h than at 2300h, which was the time when minimum responses were observed [3]. There are other studies which demonstrate circadian variations in cells involved in immune responses [4], and others describe circadian rhythms in humorally mediated responses [4,5], of the immediate hypersensitivity type. The availability, activity and toxicity of many drugs also varies with the time of administration [6,7]. The time of day that immunosuppressants are given might influence their ability to prevent or treat allograft rejection. There has been little attention paid to this possibility by those planning or reporting regimens for the treatment of patients after transplantation. Wide variations in the dose of immunosuppressants used were documented by the surveys of McGeown [8] and Kumar [9]. It seemed likely that there would also be variations in the time and frequency of administration in different units and also perhaps between individual patients in those units where strict instructions about when to take treatment are not given.

Methods

Survey of UK transplant units

Twenty-four British transplant units were sent a simple questionnaire on the details of drug treatment regimens, with particular reference to the time and frequency recommended in the unit and after discharge.
Survey of Nottingham patients

In Nottingham the policy on drug dosage at each stage after renal transplantation has been consistent, but there had been no consistent emphasis on the frequency or time of administration of this daily dose after discharge from hospital. Patients were questioned about their pattern of drug ingestion and in 35 from whom reliable information was obtained an analysis of outcome was performed.

Relationship to transplant success

The wide variation in the success of different UK units has been documented, with graft survival varying from 14—82% [10], but the information on graft survival in these units remains confidential, although the results at the two most successful units, Belfast and Oxford [11,12] are known and can be correlated with this survey.

Nottingham patients fall into two groups; those taking all drugs in the evening and those dividing the dose with some in the morning and some in the evening. The progress in the 35 patients who had satisfactory graft function at three months was analysed by plotting the reciprocal of plasma creatinine against time [13], and contrasted for the two groups, who were shown to be similar for other variables known to be important [14] other than for age: 39.7 years (15.5—57.8) in the evening only group, compared with 27.3 years (9.6—53.2) in the twice daily group (p<0.02).

Results

Survey of UK units (Table I)

A wide range of policy, and in some units a lack of policy, was revealed.

<table>
<thead>
<tr>
<th>TABLE I. UK transplant units – patterns of administration</th>
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<tr>
<td>Prednisolone</td>
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<td>Azathioprine</td>
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NB. Only the Belfast unit, with the best results in the UK, uses morning only dosing for prednisolone and azathioprine

Survey of Nottingham patients (Table II)

Several different patterns of administration were noted, with two general patterns as described above being detectable, i.e. all drugs in the evening or one or both drugs divided to include morning and evening.
TABLE II. Nottingham patients – pattern of administration

<table>
<thead>
<tr>
<th></th>
<th>Once daily am</th>
<th>BD am and pm</th>
<th>Frequency and timing</th>
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<tbody>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0</td>
<td>30</td>
<td>5</td>
</tr>
</tbody>
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**Relationship to outcome of transplantation**

**Belfast and Oxford** Publications from these units have described their results, but not the frequency and time of administration. Belfast has 82% kidney survival at one year [11] and has had a consistent policy about timing from the day after transplantation – with all patients instructed to take all immunosuppressant drugs at 1000h. This pattern of administration was not used at other units, none of which have such good results. At Oxford, another unit with better than average results [12] and also using, in at least some of their patients, lower than average doses of steroids the administration was as divided twice daily doses.

**Nottingham** The group taking evening only doses did less well, 10 out of 16 developing chronic rejection after three months, than the group taking twice daily doses in whom only four out of 19 developed chronic rejection (p<0.05). No patients took drugs only in the morning. The survival of kidneys for one to three years after transplantation in Nottingham is similar to the median results for the UK [10] with rejection and other events prior to three months being important, but late rejection appearing to be more important than in many units, including Belfast and Oxford.

**Discussion**

There is little information about whether the pharmacology of immunosuppressant drugs is different at different times, other than the many studies showing that glucocorticoids suppress endogenous production when given at the transition from activity to sleep, but much less so at the transition from rest to activity [15]. It is possible that the retention of intact adrenopituitary function, as would be expected on the Belfast regimen (morning dosing of small amounts of prednisolone) could be important in achieving good results. There are surges of glucocorticoid production by a functioning adrenal prior to waking and these might be critical. At this time immune responses may be at their most vigorous [3] and immunosuppressants may be at their lowest level in the blood. It is also the time when our calculations suggest allograft function is most frequently first affected at the start of a rejection episode [16].

Recent experiments in animals, reported in more detail elsewhere [17,18], show that the immune response used in our initial demonstrations of circadian rhythmicity can be influenced by methyl prednisolone to a variable extent,
Figure 1. The upper points represent the mean response, measured as ear swelling, 24 hours after ear challenge in sensitised rats at the time indicated [1]. The lower points demonstrate the ear swelling observed when methyl prednisolone was given at the same time as the challenge dose. All responses are influenced by methyl prednisolone, but those observed after challenge at 1000h are still greater than those at the time of minimum response in untreated animals.

dependent on the time of administration. At one time, 2200h, which is the time of onset of activity in the rat, a statistically significant immunosuppressive effect could not be demonstrated. At other times the level of significance at which an
effect of treatment could be demonstrated varied. The greatest percentage reduction in immune response (72.7%) followed treatment at 0200h. (Figure 1) which was also the only time when an effect was extended to 48 hours. At other times an effect of methyl prednisolone after the challenge was seen at 24 hours but not at 48 hours. The interpretation of these results is difficult, partly due to difficulties in comparing therapeutic effects at different times when the response being treated is itself varying with time. There are, however, also many descriptions of time-dependent variations in the action of cytotoxic drugs and corticosteroids when used in the treatment of experimental cancer and leukaemia [6,19] and these may be relevant to the use of such drugs after transplantation.

Clinicians should carefully consider whether the time and frequency of administration may be more important than has been considered up until now. Those describing treatment regimens should state the frequency and timing of drug administration, and those with experience of regimens using different timing might usefully compare their experiences. If such studies provide information to support the hypothesis, controlled trials may be needed to resolve the importance of drug timing.

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References