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# Steroids and modern immunosuppression

Immunosuppressive drugs have been used in transplant surgery units for over 20 years. It was soon found that azathioprine on its own failed to prevent rejection even in kidney transplants from living related donors.[1] A combination of azathioprine and steroids was therefore adopted, the steroids being given in high doses initially and then "tapered" over the ensuing weeks. As cortisone on its own had been shown to be ineffective in prolonging the survival of kidney transplants in dogs,[2] the evidence on which this protocol was based is difficult to discover in retrospect. Goodwin *et al* had reported a definite improvement in renal function in a patient with a renal transplant whose rejection was treated with large doses of prednisone,[3] so a period of treatment with high doses of steroids immediately after transplantation seemed a sensible approach, since rejection was very likely to occur at that time. For the next 14 years this immunosuppressive protocol was unchallenged. High doses of steroids were administered prophylactically, despite the fact that rejection was seldom suppressed altogether and that side effects were inevitable.

In 1977 McGeown *et al* reported that excellent survival of transplanted kidneys could be obtained with azathioprine and a daily maintenance dose of steroids of just 20 mg (0·3 mg/kg).[4] This dose was chosen in the belief that the wellbeing of the patient was far more important than that of the transplant, but at that time there was no experimental evidence to point to the likely outcome. Fortunately this approach was a success and it has since been supported by experimental and clinical studies which have shown that survival of the graft is not jeopardised by lowering the dose of steroids.

In rats a low dose of steroids (0·5 mg/kg a day) has been found to be just as effective as a high maintenance dose (4 mg/kg a day) when given with azathioprine to animals with a heterotopic heart graft.[5] The same has been shown in baboons, the higher dose (2 mg/kg a day) merely serving to increase the number of wound infections.[6]

Three controlled clinical trials comparing low and high dose tapered regimens of steroids have now been carried out in Britain in patients receiving cadaveric renal transplants. In Oxford[7] the starting daily doses were 30 mg and 100 mg respectively. In Cardiff the dose was 25 or 150 mg a day,[8] and in a trial in Birmingham[9] the equivalent groups received 20 mg and 75 mg a day. All patients received azathioprine in addition, and in the Oxford trial the low dose group was given 1 g of methylprednisolone intravenously on days 6, 7, and 8 after transplantation. In each of the trials the survival of grafts in the high dose group was no better than in the low dose group. All three trials reported an increased incidence of complications associated with high doses of steroids, and in the Birmingham trial mortality was increased among the patients given the higher dose. A somewhat contrary view has been taken in a report from Finland which described a comparison of two groups of 15 patients with cadaveric renal transplants.[10] The group receiving the higher dose of steroids, 3·6 mg/kg a day, fared marginally better than did those given 1·4 mg/kg methylprednisolone a day. The numbers of patients were too small to make any valid comparison, however, and in any case the dose of steroids given to the second group was not very low.

Another factor may be the time of day when immunosuppressive treatment is taken, which may be important because of diurnal variations in the endogenous production of steroids.[11] One survey of British kidney transplant units showed a variation in dosing from alternate days to three times a day.[12] The Belfast unit, which has the best results in Britain, is the only one using a single morning dose of azathioprine and prednisolone. There is little experimental evidence to indicate that this might be the optimal regimen: in rats, for example, a continuous infusion of prednisolone has given better immunosuppression than has the same dose delivered as a single daily dose.[13] Nevertheless, this point needs clarification, and a controlled trial is required to compare daily and twice daily dosing in patients who have received a first cadaveric kidney transplant.

Alternate day treatment has also been advocated as a way of avoiding the complications associated with treatment with prednisolone, particularly in children. Uncontrolled studies suggest that alternate day treatment can provide adequate immunosuppression, but whether such treatment yields fewer complications is less certain.[14,15] A controlled trial has recently been reported by Dumler *et al* which found less osteonecrosis of the hip in those patients randomised to an alternate day regimen.[16] Since, however, all the patients were initially treated with high doses of daily steroids a simple reduction in the starting dose might have had a similar effect.

One other aspect of maintenance immunosuppression that bears examination is that of prescribing a large dose of steroids at the time of the transplant operation. This seems to be a universal practice in kidney and heart transplant units—even those using low dose maintenance steroids. Experimental

justification for this practice is difficult to find, though it does seem to prolong survival of cardiac allografts in rats.[17 18] In a double blind controlled clinical trial, Kauffman *et al* have shown that 1 g of methylprednisolone given at the time of cadaver kidney transplantation contributed nothing to survival of the graft.[19] Since, however, these patients also received high maintenance doses of steroids, the conclusions might not apply to patients on a low dose regimen.

Current evidence suggests that patients with functioning transplants need to take their immunosuppression indefinitely, since stopping treatment has occasionally led to rejection of the graft.[20 21] Although azathioprine may sometimes be discontinued without jeopardy, small doses of steroids (at least 7 mg a day) seem to be needed for an indefinite period.[22]

When a transplanted organ is being rejected despite the regular administration of immunosuppressive agents the episode can often be halted and reversed by increasing the dose of steroids. Ten years ago intravenous methylprednisolone came to be used in kidney transplant units in place of a rise in the oral dose of prednisolone. Initial reports were very favourable,[23] and rejection appeared to be more easily reversed than with oral steroids.[24] In rats, however, the two forms of treatment give similar results,[25] and two controlled clinical trials have now been published which confirm the similarity in outcome in man, with oral steroids scoring mainly on the basis of cost.[25 26] Laboratory studies have shown that an intravenous dose of steroids has no more suppressive effect on the mixed lymphocyte culture than the same dose taken orally.[27]

The optimal dose needed to reverse a rejection episode remains an unanswered question. An oral dose of 3 mg/kg a day is customarily used and is generally effective. The usual dose of intravenous methylprednisolone is 16 mg/kg a day, and this is probably excessive: in a randomised double blind study of 64 patients who had received kidney transplants those who suffered rejection responded as well to 3 mg/kg of methylprednisolone a day as to 30 mg/kg, a dose which was associated with a greater number of infections.[28]

Until recently steroids were thought to be the only drugs that could reliably reverse rejection episodes. Now there appears to be an alternative—namely, antilymphocyte globulin. A short course of intravenous antilymphocyte globulin has sometimes been effective when steroids have failed to halt rejection,[29] and a controlled trial in patients receiving cadaver renal transplants has shown that antilymphocyte globulin can be used in place of steroids with as good, if not better, results.[30] These findings have prompted at least one kidney transplant unit to use antilymphocyte globulin routinely in place of steroids for the management of rejection.[31]

Cyclosporin A has been under trial in transplant centres for nearly five years, and its general introduction is now imminent. The early trials on patients given renal transplants showed that a combination of cyclosporin and conventional treatment caused overimmunosuppression and the appearance of lymphomas.[32] This has also been found in monkeys with cardiac transplants.[33] Unfortunately, in human cardiac transplantation cyclosporin does not appear to be sufficiently immunosuppressive on its own to suppress rejection, and some sort of combination drug treatment is required. This again has resulted in some patients developing lymphomas,[34] but cyclosporin and a low dose of prednisolone may provide a satisfactory compromise.[35] Although such a combination is no more immunosuppressive in dogs than cyclosporin alone,[36] this regimen has been adopted by a number of centres performing clinical renal transplantation, particularly in the United States. In Europe the emphasis has been on using cyclosporin on its own, and in a controlled clinical trial carried out in eight European renal transplant centres the patients given cyclosporin did better than did the control group treated with azathioprine and steroids.[37] Rejection was quite often a problem, however, and ultimately 73% of the patients required steroids at one time or another. Assuming that steroids are needed with cyclosporin (and this has still to be shown in a controlled clinical trial) then the precise dose will need to be established soon to avoid some potentially toxic regimen being adopted as a world standard. The regimen that has been used so successfully by Starzl *et al*[38] had a starting steroid dose of 200 mg, which was decreased daily to a maintenance dose of 20 mg a day by the sixth day after transplantation. Though this "tapered" regimen was not overtly toxic it may have been unnecessary—for reasons already discussed.

The immunosuppressive protocols using high doses of steroids that have been popular in the last two decades have undoubtedly been responsible for much of the considerable morbidity and mortality that have accompanied transplantation. Many transplant units have now changed to low dose regimens, with no evidence to date that survival of grafts has suffered as a consequence. Though steroids may still be needed in combination with cyclosporin, the minimum effective dose must be found from controlled studies before an unnecessarily high dose is adopted as a standard for the future.

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# Chronic headaches in general practice

In one week a busy general practitioner may see between 10 and 20 patients complaining of headaches—a total of 500 to 1000 a year. If he is worried that each one may have a cerebral tumour he will have a lot of worried patients. The fear of missing a primary cerebral neoplasm is unnecessary, however, because these tumours are rare—2500 a year in the whole of Britain. In an average practice of 3000 to 4000 patients one such tumour should be seen in five to 10 years. Furthermore, a brain tumour replaces normal tissue and gives rise to progressive neurological deficit or epilepsy, or both; headache alone is uncommon. "A headache of more than one year's duration without physical signs is not due to a structural lesion" is a useful aphorism of the late Sir Charles Symonds, a great neurologist with a vast clinical experience and a mammoth memory. Beware of the headache that has changed in character, however; it then becomes a new and recent headache.

How, then, does one tackle the common problem of chronic headaches? "Common things commonly occur" and 90% of chronic headaches fall into one of four categories: migraine, tension headache, muscle contraction headache, or a combination of two or more of these. (Against current teaching, I do not believe that tension and muscle contraction headaches are synonymous. As defined below, they are different conditions requiring different treatment. This is not a new idea,[1] but doctors may be deluded by techniques—electromyography in this instance.[2])

Next, I recommend learning definitions, rigidly applying these to patients seen in the surgery, and only reluctantly adding variations. The following definitions have been proposed.[3]

Migraine headache is an episodic headache accompanied by visual or gastrointestinal disturbances, or both; the attacks last for hours with total freedom between episodes. Before the headache visual symptoms occur as an aura, and during it photophobia may be present; alimentary symptoms consist of nausea and vomiting. If there are no visual but only gastrointestinal disturbances then vomiting must feature in some attacks.

Tension headache is a continuous symmetrical headache, often described as a pressure, an awareness, or discomfort at the vertex, forehead, occiput, in a coronal distribution, or all over the head, and not associated with visual or gastrointestinal disturbances. The ache occurs daily, lasts many hours, frequently throughout the waking period, rarely interfering with everyday activities, and is unaffected by analgesics but may respond to sedatives. Typically the patient complains of "a band round my head as if I am wearing a hat," or "a pressure, like a weight on top of my head."

Muscle contraction headache is a painful tender muscle or muscle spasm adjacent to a painful site—for example, cervical spondylosis, an impacted wisdom tooth, or the temporomandibular joint. The pain is accentuated by movement of the muscle and often relieved by heat, cold, or analgesics. Treating the underlying cause gives partial or complete relief of symptoms.

Difficulties arise with a mixture of two or three of these common headaches. Then the doctor has to analyse each headache in turn, which may take 15-20 minutes—not possible during a busy evening surgery and a special appointment may be necessary. In a recent series of 100 patients referred to two neurologists interested in headaches and migraine, 53 had migraine alone; 26 had migraine and tension or muscle contraction headache; 16 had tension or muscle contraction headaches, or both; three had migrainous neuralgia (cluster headache); and two were not diagnosed at the initial consultation.[4] But these were difficult cases, often undergoing their second referral for consultant opinion.

The importance of making the right diagnosis is to determine the line of treatment. Tension headache as defined above is usually due to anxiety, depression, or agitated depression and requires treatment along psychiatric lines. Muscle contraction pain is helped by a dental surgeon, a physiotherapist, or other appropriate physical treatment. The management of migraine has recently been outlined.[3]

How does the busy general practitioner cope with these chronic headaches? Most cases can be diagnosed in three to four minutes of history taking. Although I have described 15 questions of pain analysis,[5] the spontaneous remarks by the patient, followed by a few direct questions about timing,