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Progress report

Corticosteroids in liver disease: possible mechanisms of action, pharmacology, and rational use

Since the original publications by Hench and his colleagues[1] [2] on the use of cortisone and ACTH in the treatment of rheumatoid arthritis, corticosteroid drugs have assumed an important role in the therapy of a large number of diseases, including diseases of the liver and gastrointestinal tract. Although the precise mode of action of these agents is uncertain, there is increasing evidence that their beneficial effects result from actions on immunological and inflammatory processes. An understanding of such effects and of the clinical pharmacology of the corticosteroid drugs should lead to a more rational approach to therapy. This is particularly important in treating patients with liver disease who are prone to the unwanted effects of corticosteroid therapy and in whom the metabolism of these drugs may be altered.

The aims of this paper are threefold: firstly, to outline the biochemical pharmacology of the corticosteroid drugs relevant to the clinical management of gastrointestinal and liver disease; secondly, to review current knowledge of the immunological and anti-inflammatory effects of these agents; and, thirdly, to discuss the use of prednisone and prednisolone in the management of a number of hepatic diseases. Although the basis of therapy of corticosteroids is probably similar in gastrointestinal and liver diseases, the indications for the use of corticosteroids in gastrointestinal diseases are less clearly defined and are not discussed here.

Pharmacology of corticosteroid drugs

Various biochemical manipulations of the corticosteroid molecule have resulted in differing glucocorticoid or mineralocorticoid activity, but cumulative toxic effects remain the major problem of long-term corticosteroid therapy. Corticosteroids have been shown to interact with receptor proteins in the cytoplasm of cells[3] and alteration of protein synthesis follows interaction of the glucocorticoid: receptor complex with nuclear DNA.[4] However, it has been proposed that corticosteroids have effects on cells that are mediated through other mechanisms. One such mechanism postulates alteration of cell surface characteristics, and this may be responsible for the rapid alterations in lymphocyte kinetics observed after the administration of corticosteroids.[5] For instance, corticosteroids have been shown to alter the expression of cellular IgG and complement receptors, and the locus of action in these studies appears to be at the membrane level.[6] Studies using lysosomes also support a direct action at membrane level.[7] Complex interactions between cyclic nucleotides and glucocorticoids on the physiology of cells have been demonstrated.[8] Although cAMP does not act as an intracellular 'second message' for the mediation of glucocorticoid action, cortisol

has been shown to activate adenyl cyclase in human leucocytes[9] [10] and this may have a significant influence on the state of activation of these cells, especially those of the monocyte/macrophage system.[11]

Prednisone has very little intrinsic glucocorticoid activity,[12] and has to be converted in the liver to the biologically active metabolite, prednisolone. In severe liver failure some impairment of this conversion may occur, but it is comparatively trivial.[13] In a detailed pharmacokinetic study, Schalm and his colleagues[13] showed that serum prednisolone levels were significantly lower in patients with impaired liver function than in others, but there was also a greater percentage of pharmacologically active, unbound drug present in the serum under such circumstances. An additional factor to be taken into account in this situation is impairment of hepatic A ring reduction, resulting in decreased elimination of the active metabolite.[14] [15] Thus, impaired conversion of prednisone to prednisolone in severe liver failure may be compensated for by a decreased rate of elimination of the active metabolite as well as by decreased protein binding.

Schalm and his colleagues concluded that failure of some patients with chronic hepatitis to respond to prednisone treatment could not be attributed to the small differences in conversion of prednisone to prednisolone associated with severe impairment of liver function. However, there are occasional individuals who show a marked impairment in the conversion of prednisone to prednisolone,[14] and most authors accept that it is probably best to administer prednisolone rather than prednisone to all patients with liver disease, if only because the serum levels achieved are more predictable.

The elimination half-life of prednisolone from plasma remains constant ($3{\cdot}5 \pm 0{\cdot}2$h) over the conventional dosage range (5–100 mg) and this closely correlates with the tissue half-life which is approximately one and a half to twice the plasma elimination half-life.[16] It is the tissue half-life which most closely relates to therapeutic efficacy and long-term toxic effects.[16] Absorption of prednisolone appears to be virtually complete even in the presence of mucosal damage[17] or when administered concurrently with antacid medications.[18] Over the conventional dosage range, protein binding is unchanged with a constant amount bound to cortisol binding globulin (CBG), most of the remaining prednisolone being bound loosely to other serum proteins with approximately 10% predisolone unbound. In hypoalbuminaemic states a greater proportion of prednisolone is unbound and this may result in severe metabolic consequences.[19] This has led some workers to derive a formula for adjusting prednisolone dose on the basis of serum protein levels.[20] As the appropriate dose is arbitrary and difficult to predict, this further refinement seems unnecessary. It should be noted that the binding affinity of the prednisolone for the intracellular glucocorticoid receptor is very much higher than that for albumin and probably that proportion not bound to CBG is metabolically active, not merely the free drug.[8] A recent publication has shown that the glucocorticoid fraction in plasma that is available for transport is not restricted to the free fraction, but includes the larger albumin-bound moiety.[21] It has also been observed by different workers[22] [23] that alterations in the metabolic clearance rate of corticosteroids can have an influence on the therapeutic effect and it has been suggested that long-term daily therapy with corticosteroids results in the induction of corticosteroid metabolism and consequent loss of effect.[22] This effect, if present, is likely

to be slight and to have little influence on therapy. It has, however, been shown that simultaneous administration of potent microsomal enzyme-inducing drugs such as diphenylhydantoin,[24] phenobarbitone,[25] or rifampicin[26] can result in a marked increase in the metabolic clearance of prednisolone with consequent loss of therapeutic effect. Other drugs with a similar enzyme-inducing potential are likely to have a similar influence on prednisolone kinetics.

Anti-inflammatory effects and changes in immune system mediated by corticosteroids

Corticosteroids cause a wide variety of anti-inflammatory effects and changes in the immune system. These are considered here before a discussion of the clinical use of these agents in specific diseases. As there is considerable overlap between anti-inflammatory and anti-immune effects, these are considered together here. With respect to the immune system, most of our current knowledge indicates that it is chiefly cell-mediated immune function rather than the humoral components of the defence mechanisms that are altered by corticosteroid therapy. After the administration of corticosteroids, there is a blood neutrophil leucocytosis that reaches a peak four to six hours after the drug has been given.[27] At the same time, there is a decrease is the circulating numbers of lymphocytes,[28] monocytes,[29] and eosinophils.[30] The depletion in circulating numbers of monocytes, lymphocytes, and eosinophils is transient and counts return to normal after 24 hours except after single massive doses of methylprednisolone[31] (>1g). This pattern is not peculiar to isolated single doses of corticosteroids but occurs on a daily or alternate-day basis for as long as several years.[32] Hence, the cytopenia is not cumulative; the kinetics are related to each administration of corticosteroids, except when the dosage interval is less than 24 hours.

With regard to neutrophil function, the most important effect is the inhibition of their ability to accumulate at an inflammatory focus[33] this is a result of inhibition of chemotaxis[34] and of inhibition of leucocyte adherence to blood vessel walls.[35] Neutrophils from patients receiving corticosteroids demonstrate normal phagocytic and bactericidal functions,[5] although very high concentrations of corticosteroids can suppress these functions also. Monocyte chemotaxis is similarly impaired in the presence of corticosteroids[36] although monocytes isolated from subjects on corticosteroids exhibit normal chemotactic responses *in vitro*.[29] Monocyte bactericidal activity is depressed by corticosteroids.[29] However, the most important aspect of monocyte function that is altered by corticosteroids is their ability to respond to lymphokines. These are chemical messengers liberated by lymphocytes on exposure to certain antigens and mitogens, and they modify the behaviour and recruitment of other cells involved in the immune response. Some of the most important lymphokines identified alter monocyte activity such as migration inhibition factor (MIF), macrophage arming factor (MAF) and macrophage chemotactic factor (MCTF). There is evidence that, in general, lymphokine production is uninfluenced by corticosteroids,[37 38] although some work suggests that corticosteroids can depress the production of certain lymphokines, in particular macrophage chemotactic factor.[39] However, the ability of monocytes to respond to liberated lymphokines is markedly suppressed.[37 38] This may be mediated by alterations in the surface

receptors of the monocyte.

As indicated above, corticosteroid administration causes a transient lymphocytopenia with counts returning to normal by 24 hours.[28] There is a decrease in both T and B lymphocyte numbers, although there is a disportionately greater decrease of circulating T lymphocytes.[28] This depletion almost certainly represents redistribution into other body compartments rather than lysis.[40] Some subpopulations of lymphocytes may show differing sensitivities to corticosteroids, as it has been shown that circulating 'null' cells (lymphocytes with neither E nor EAC surface markers) are not decreased after prednisone administration.[41] It has also been noted that there are differential effects of different corticosteroid preparations on lymphocyte function. For instance, dexamethasone administration results in suppression of PHA-induced cellular cytotoxicity when lymphocytes are assessed four hours after administration; yet equivalent 'anti-inflammatory' doses of prednisone or hydrocortisone fail to produce this suppression.[41] This may reflect the different plasma half-lives and different receptor affinities of the various preparations.[41] Lymphocyte responses to antigen (purified protein derivative of *M. tuberculosis*, PPD) are suppressed only during chronic administration of corticosteroids.[42] Mitogen (phytohaemagglutin, pokeweed mitogen, concanavalin A) responses appear to be unaltered.[42] Conflicting results on these responses[43] may have represented a profound depletion of monocytes necessary for the *in vitro* response to antigens. Although macrophage migration inhibiting factor (MIF) and macrophage arming factor (MAF) are released normally by lymphocytes, the monocyte-macrophage response to these liberated factors is impaired in the presence of corticosteroids.[37 38] One illustrative consequence of this may be the reduction of delayed skin reactivity in patients on corticosteroids. Additional effects of corticosteroids that have been demonstrated include impairment of particulate antigen processing by macrophages,[44] and diminution of T lymphocyte cytotoxic activity by prior exposure of these cells to corticosteroids.[45] This latter effect has been shown to be independent of RNA, DNA, or protein synthesis and is reversed by subsequent exposure to concanavalin A. This suggests that the site of action of corticosteroids in this situation is at the membrane level, being independent of glucocorticoid receptor interaction.

In summary, the circulation kinetics and access of leucocytes to sites of potential immunological reactions are suppressed and the interaction of effector cells with the soluble products of activated lymphocytes are antagonised, resulting in marked suppression of cell-mediated immune responses. The influences of corticosteroids on monocytes and lymphocytes are sum-

Table 1 *Influence of corticosteroids on lymphocyte and monocyte function*

	Recognised effects	*Probable effects*
Monocytes and macrophages	Decreased numbers in circulation[29]	Antigen processing inhibited[44]
	Decreased access to inflammatory sites[46]	Decreased reponse to chemotactic factors[36]
	Decreased bactericidal capacity[29]	Lysosomal stabilisation[53]
	Decreased reticuloendothelial system clearance[47]	
	Decreased response to MIF and MAF[37]	
Lymphocytes	Reduced circulating numbers[28]	Normal mitogen responses[43]
	Decreased antigen blastogenesis[42 43]	Inhibition of release of MCTF[32]
	Normal release of MIF and MAF[38]	
	Reduction of T cell cytotoxicity[45]	

MIF: migration inhibitory factor. MAF: macrophage arming factor. MCTF: macrophage chemotactic factor.

marised in Table 1.

Antibody synthesis is not influenced by corticosteroids, although this does depend on the timing of corticosteroid administration in relation to the antigenic challenge. With the exception of high doses of methylprednisolone, serum immunoglobulin concentrations are not altered.[49] All complement component serum levels may be reduced to a variable degree by corticosteroid therapy.[50]

Some actions of corticosteroids are predominantly anti-inflammatory, such as their influence on vascular permeability,[51] and their alteration of the response to local mediators of inflammation such as kinins[52] and histamine,[48] but other influences are predominantly immunosuppressive (Table 2).

Table 2 *Anti-inflammatory and immunosuppressive effects of corticosteroid therapy*

Predominantly anti-inflammatory effect	*Predominantly immunosuppressive effect*
Vascular stabilisation[51]	
Altered responsiveness to kinins[52] and histamine[48]	
Decreased neutrophil accumulation[33 34 35]	
Decreased neutrophil function[5]	
	Decreased complement levels[50]
	Monocytopenia,[29] eosinopenia[30]
	Lymphocytopenia[28]
	Decreased lymphocyte and monocyte function (Table 1)

Although immunosuppressive activity may result in anti-inflammatory activity, the importance of either influence remains to be elucidated in many disease states.

A separate effect that may have some relevance in human liver disease is the suppression of collagen formation by inhibition of proline hydroxylase activity.[54] Although this has been demonstrated in experimental liver injury, no studies to date have shown that this is of significant clinical benefit to man.

With regard to hepatitis, the role of infiltrating mononuclear cells as the cause of cell death has been pursued in a number of studies. Lymphocyte cytotoxicity for a variety of liver cell lines in tissue culture has been demonstrated in chronic active liver disease (CALD), although this has not been shown to be a specific finding (see review by Smith, C.J. *et al.*[55]) However, it does seem likely that lymphocytes from patients with a variety of liver disorders are sensitised to one or more antigens found in normal liver tissue. Lymphocytes from patients with alcoholic hepatitis have shown '*in vitro*' cytotoxicity for rabbit hepatocytes, possibly reflecting sensitivity to a liver-specific membrane lipoprotein.[56] It may therefore be relevant that corticosteroids have been shown to diminish lymphocyte cytotoxic activity.[45]

A recent paper has provided evidence that mononuclear phagocytes already recruited into the liver by other processes may release factors toxic for hepatocytes on exposure to endotoxin, thus perpetuating tissue injury.[57] The ability of endotoxin to activate macrophages in this situation may be reduced by corticosteroids, as these drugs have been shown to protect against endotoxin-induced shock.[58] Thus it may be appreciated that corticosteroid therapy in liver disease may influence the course of the illness through a wide variety of anti-inflammatory and immune mechanisms, and, until precise knowledge of the pathogenesis of these diseases is apparent, the mechanism of action of corticosteroids remains speculative.

Effect of prednisolone on normal hepatic function and tests of liver function
In the hepatic conditions to be considered, the influence of prednisolone on the course of the illness has been judged either on clinical grounds or on the basis of changes in biochemical tests. This latter area has been investigated in normal subjects,[59] and, although there was a significant decrease in the conjugated bilirubin concentration during prednisolone treatment, there was no alteration in quantitative tests of liver function (galactose elimination capacity, bromsulfphthalein transport maximum and storage capacity). There was a significant rise in GPT and IgM concentrations, but no value became abnormal. All other enzymes and serum proteins remained unchanged during prednisolone therapy. Urinary D-glucaric acid output also remained unchanged, suggesting that prednisolone had little effect on the state of hepatic enzyme induction. Although caution should be exercised in extrapolating these results to patients with chronic liver disease, they show that prednisolone administration does not appear to interfere with the interpretation of these tests.

Use of corticosteroids in liver disease

VIRAL HEPATITIS

As early as 1937, it was suggested by Eppinger that adrenal cortical hormones might be beneficial in the treatment of hepatic diseases. Initial studies of the use of corticosteroids in viral hepatitis indicated that they might be of some benefit,[60] [61] but as early as 1953 it was suggested that this form of therapy made the patient more vulnerable to relapse.[62] Of 117 control patients, none relapsed, whereas two of 10 patients treated with cortisone relapsed. Although these figures are unbalanced and retrospective, this study has been subsequently confirmed in a paper from Switzerland, where a relapse rate of 15% was noted in the steroid-treated group (101 subjects) as against 1% in the placebo group (275 subjects)[63]. In addition, the steroid-treated group were more prone to peptic ulceration and pyogenic infections. A feature of all these early studies was the more rapid resolution of raised serum levels of bilirubin in the steroid-treated groups. A case has been made by a number of authors for the treatment with corticosteroids of viral hepatitis with prolonged cholestasis as the period of jaundice is shortened. The opposing view has been expressed, but review of the biochemistry and histology of the patients in this report[66] suggests that at least two of the four patients studied had chronic active hepatitis. Relapses are likely if the steroids are withdrawn too soon and treatment, if instigated, should be continued well into convalescence and until the serum bilirubin level is normal.[64] With the exception of prolonged cholestasis, corticosteroids are contraindicated in uncomplicated viral hepatitis.[67]

FULMINANT HEPATITIS

There has been considerable controversy over the years concerning the place of corticosteroids in the management of fulminant hepatic failure. In 1962 it was reported that corticosteroids might have a favourable influence on the outcome of patients with acute hepatitis in coma,[68] but other reports were unable to confirm these findings.[69-71] In 1976 a double-blind prospective study of the use of methylprednisolone in severe viral hepatitis was published and the authors concluded 'that corticosteroid therapy did not enhance

survival in patients with severe viral hepatitis and that it may be deterimental[72]. In the ensuing correspondence there was some criticism of the comparability of the two groups and of the fact that survival in the placebo group was over 80%.[73] This figure suggests that these were not patients with fulminant hepatitis but that they had a less severe form of hepatitis. However, other correspondence has provided additional figures on survival in other groups of patients with support for the contention that corticosteroids are of no value in fulminant hepatitis.[71] The likelihood of a type II statistical error in this study[72] is very small indeed. In a preliminary report from the USA Acute Hepatic Failure Study Group,[74] no benefit for corticosteroid therapy has been demonstrated after analysis of the results from the first 57 patients randomised and considered eligible. A smaller unblinded, European multicentre study[75] has produced similar results. Survival was 12% in the corticosteroid-treated group (26 subjects) compared with 14% in the placebo group (14 subjects). Although there are differences in disease severity, entry criteria, and therapy in all these studies, the general consensus at present is firmly against the use of corticosteroids in fulminant hepatitis. Indeed, combining results from the four randomised trials[70 71 72 75] gives strong evidence of a negative effect ($P < 0{\cdot}02$).

CHRONIC ACTIVE HEPATITIS

There have been three major studies published in the past 10 years demonstrating a beneficial effect of corticosteroids in chronic active hepatitis (CAH), both in terms of disease activity and of mortality.[76-78] Unfortunately, the meaning of the term 'chronic active hepatitis' has evolved since the instigation of these studies, and current criteria are still not uniformly accepted. What was originally a clinical term referring to symptomatic patients with both chronic and active hepatocellular disease has now become a term applied on the basis of characteristic hepatic histological features, whatever the clinical context. We are also aware of a number of predisposing factors, especially certain drugs, that were not apparent 15 years ago.

In chronic active hepatitis, a number of abnormalities of cell-mediated immunity (CMI) have been documented (see review[55]). These include sensitivity to crude liver homogenates, and to more highly purified liver antigens such as human liver-specific protein (LSP or HSP).[79 80] Lymphocyte cytotoxicity to liver cells in tissue culture has been demonstrated, although this is not specific for chronic active hepatitis. These changes in cell-mediated immunity may parallel disease activity,[81] and it is tempting to suggest that the beneficial effect of corticosteroids is mediated through their known effects on cell-mediated immunity. It should be noted that it has been postulated that poor CMI responses to HBsAg may result in HBsAg persistence (the chronic carrier state), a normal response resulting in acute hepatitis and HBsAg clearance.[82] If this is correct, early exhibition of corticosteroids in HBsAg-positive hepatitis might result in chronic disease and a protracted carrier state. However, this has never been convincingly demonstrated to occur in human disease. It has been stated that HBsAg-positive disease runs a more benign course and responds to corticosteroid therapy less frequently, and a recent abstract supports this contention.[83]

The Mayo Clinic has reported that two-thirds of a group of patients with CAH being treated with steroids suffered one or more serious complications

of steroid therapy.[84] It therefore seems that those patients in whom the benefits of steroid therapy outweigh the incidence of serious side effects need to be precisely defined.

It should be noted that, of the three widely quoted trials,[76-78] only two were able to test for HBsAg and that the incidence of this marker was surprisingly low, probably reflecting the relatively insensitive methods of detection available at the time. In the quoted trials, and especially the Mayo Clinic study, a large number of patients were symptomatic and a large proportion were cirrhotic at the time of entry to the study. In addition, the biochemical abnormalities required for entry to this study showed that this group had particularly severe disease (AST 10 × normal or AST 5 × normal, together with a serum γ globulin level 2 × normal). This is in contrast with the present situation, where a substantial proportion of patients diagnosed as having CAH are asymptomatic[85] and pre-cirrhotic with less markedly abnormal biochemical parameters.

However, all of the above three studies of corticosteroid therapy of patients with CAH arrived at similar conclusions, and in an elegant analysis of these studies Wright *et al.* come to the conclusion 'that corticosteroid therapy only outweighs its potential toxicity in those who are symptomatic, who are HBsAg-negative and who have severe histological abnormalities (subacute hepatitis with multilobular necrosis or active cirrhosis)'[86]. The risk to benefit ratio is unknown in patients who are HBsAg-positive or clinically well persons and routine administration of corticosteroids to these subgroups may not be justified. However, each patient needs to be assessed on an individual basis, as there may well be a number of patients in these categories who benefit from steroid therapy.

In those patients with chronic active hepatitis who benefit from steroid therapy, it has been shown that a daily combination of prednisone (10 mg) and azathioprine (50 mg) after an initial month of higher prednisone dose offers the best chance of disease control combined with the lowest incidence (10%) of major steroid side-effects.[84] Current advocacy of alternate day steroid regimes has led to their assessment in this condition. Titration of alternate day dosage to secure biochemical and clinical resolution does increase early survival, but the incidence of severe complications is considerably higher (36%) than in the group treated with the fixed combination outlined above.[84] In addition, histological resolution of the disease occurred less frequently in the 'alternate day' treated patients. A recent study recommends the use of prednisolone rather than prednisone, as the serum levels are more predictable.[14]

Relapse tends to be treated in an empirical manner, and additional studies are necessary to determine the appropriate use of corticosteroids in this situation. However, it has been shown that 50% of those with severe disease will relapse if corticosteroids are discontinued within six months of remission induction, whereas the relapse rate falls to 8% if treatment is continued beyond six months.[84 87] It seems that only a minority require continuous steroid therapy for longer than three years,[88] but guidelines have still to be precisely determined.

Late results of the outcome of treatment with corticosteroids of an early group of patients have recently been published by the Royal Free group in abstract form.[89] The mean duration of treatment with corticosteroids was 4.5

years. Age, presence of antinuclear factor, cirrhosis, or level of transaminases at presentation were not prognostic factors, although male patients untreated did less well than female patients. Ten-year survival in the treatment group was 63%, compared with 27% in the control group ($P=0{\cdot}03$) with a median survival of 12·2 years in the former group, compared with 3·3 years in the latter.

CHRONIC PERSISTENT HEPATITIS

There is general agreement that corticosteroid therapy is not indicated in those patients with chronic persistent hepatitis, as the condition is virtually asymptomatic, non-progressive, and associated with a good prognosis.[90] However, sampling error on liver biopsy can lead to an erroneous diagnosis in a patient with chronic active hepatitis. Regular follow-up should be encouraged, especially for symptomatic patients, those with transaminase concentrations greater than five times normal, and those with serum markers of past or present hepatitis B infection. Progression of chronic persistent hepatitis to chronic active hepatitis has been documented especially in those patients presenting with symptoms of insidious onset and with markers of past or present hepatitis B infection.[91] The use of corticosteroids in this situation is unlikely to be of clinical benefit, both because of the relative mildness of the illness and because of the association with markers of hepatitis B infection.[83 86] In the two subjects treated with corticosteroids in the study quoted above,[91] no histological change had been observed after a year's treatment.

ALCOHOLIC LIVER DISEASE

Investigations into the short-term use of corticosteroids in alcoholic liver disease have been concerned with the syndrome of alcoholic hepatitis, partly because of the high mortality (40%) and partly because patients with this condition demonstrate various immunological abnormalities that may be responsive to corticosteroid treatment. It has been demonstrated that circulating T lymphocytes from patients with alcoholic hepatitis react to alcoholic hyaline[92] and show *in vitro* cytotoxicity to rabbit hepatocytes.[56] There is also a reversible depression of delayed cutaneous hypersensitivity in alcoholic hepatitis.[93] These alterations in immunological reactivity suggest a rational basis for corticosteroid therapy. It has been proposed that corticosteroids might shorten the duration of the illness, reduce the mortality and the incidence of subsequent cirrhosis. A large number of clinical trials have been published[94-101] and almost all have shown no significant benefit in terms of mortality, although various biochemical measures improved more rapidly on steroid therapy. Two of these studies[95-99] demonstrated a benefit with the administration of corticosteroids and further analysis of this suggests that there might be a subgroup of patients with alcoholic hepatitis who do benefit from the administration of corticosteroids. It seems that this group is represented by those with clinical criteria suggestive of the diagnosis of alcoholic hepatitis who also have either hepatic encephalopathy or a coagulation disorder precluding liver biopsy. In one trial published[96] that has studied this particular subgroup, only 20 patients were randomised, and although there was a trend to better survival in the steroid-treated group, no statistical difference was noted. There is a high degree of probability of a type II error

in this particular study. Another trial studying this subgroup shows a definite advantage for the steroid-treated group.[99] Conn, in an editorial on the subject,[102] has outlined the various pitfalls in either the randomisation procedures, the exclusion process, or the experimental design, all of which might have led to unwanted bias in the interpretation of the results. In this editorial, Conn states that there was no evidence to support the use of corticosteroids in the routine treatment of alcoholic hepatitis, but that there may be a subgroup with severe alcoholic hepatitis and encephalopathy who may benefit. Data extracted from the published studies on the relevant subgroup suggests a definite advantage (see review by Tolman and Powell),[103] but until a large randomised double-blind study has been completed and published the answer remains uncertain. There is general agreement that steroids are of no benefit in those patients with only mild to moderate disease—that is, without encephalopathy.

It has been stated that, in those who have been treated with steroids, a course of high-dose steroid therapy (40–60 mg prednisolone daily) lasting four to six weeks is sufficient, with gradual reduction of the dose after this time. If a short-term benefit is convincingly demonstrated, the uncertainty that remains is that in those patients treated with steroids there is the possibility that steroid therapy merely delays the patient's eventual death. One study has commented on the high incidence of mortality in the steroid-treated group after completion of the study.[100] The scanty evidence available on the development of cirrhosis suggests that steroid therapy has no influence on the eventual development of this complication.

Miscellaneous liver diseases

Because of the known immune associations with primary biliary cirrhosis, corticosteroids have been used in this condition. However, no convincing benefit has been demonstrated,[104] and, indeed, the skeletal effect of corticosteroids, together with the known incidence of osteomalacia and oestoporosis in this disease[105], contraindicates them.

Granulomatous hepatitis is a curious entity[106] that is usually a diagnosis of exclusion, although more causes of hepatic granulomata are being recognised. The association of a chronic febrile illness with hepatic granulomata in the absence of a known cause is often designated granulomatous hepatitis. In some patients it may represent an atypical form of sarcoidosis.[107] Dramatic clinical and biochemical responses to corticosteroid therapy have been noted and alternate-day therapy appears to maintain control successfully.[108] This is a rare condition and the small numbers in the studies published do not allow more specific guidelines.

Corticosteroids are of benefit in those multi-system diseases that occasionally involve the liver, such as polyarteritis nodosa or systemic lupus erythematosus. Corticosteroids have been used in Wilson's disease, Gilbert's disease, Dubin Johnson syndrome, and hepatic amyloidosis and have been shown to be of no value.

Summary of clinical use of corticosteroid drugs in liver disease

The pharmacokinetics of corticosteroids are similar over a wide dosage range, and although there are minor variations in conversion of prednisone to prednisolone in severe liver disease this is unlikely to alter therapeutic

efficacy. Prednisolone administration, however, results in more predictable serum levels. Enzyme-inducing agents, in particular diphenylhydantoin, phenobarbitone, and rifampicin, may markedly reduce the therapeutic efficacy of steroids.

There is an established place for steroid therapy in the management of the symptomatic and histologically severe forms of chronic active hepatitis. However, the use of corticosteroids in hepatitis B-positive CAH is still controversial. Corticosteroids are of no benefit in fulminant hepatitis, whatever the aetiological agent, and may well be detrimental in this situation. If they have a place in the management of alcoholic liver disease, it will be confined probably to those patients with alcoholic hepatitis who have encephalopathy or a severe coagulation disorder. There is a very limited role for their use in viral hepatitis with prolonged cholestasis, although there is an increased risk of relapse with this therapy. Corticosteroids often have a dramatic effect on patients with granulomatous hepatitis, but in a large variety of other hepatic diseases they have been demonstrated to be of no benefit.

*Address for reprint requests:
Professorial Medical Unit,
Level F, Centre Block,
Southampton General Hospital,
Southampton, SO9 4XY, England

*A. R. TANNER AND L. W. POWELL
Department of Medicine
University of Queensland
Royal Brisbane Hospital
Brisbane
Australia 4029

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