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Systemic steroids in chronic severe asthma

The introduction of potent topically active inhaled steroids (beclomethasone dipropionate or betamethasone valerate) in the early 1970s reduced the number of asthmatics prescribed systemic steroids.[1] A few patients with severe chronic asthma still, however, require both forms of treatment.[2,3]

The choice of steroids for systemic use includes a range of glucocorticosteroids from natural cortisol (hydrocortisone) to various synthetic fluorinated cortisol analogues such as dexamethasone and betamethasone. When these are compared for anti-inflammatory activity with hydrocortisone on a milligram to milligram basis prednisone and prednisolone are four times as potent; methylprednisolone and triamcinolone (9α-fluorohydroxyprednisolone) five times; and dexamethasone and betamethasone 25 to 30 times as potent.[4,5]

Prednisone itself is inactive and requires conversion by hepatic hydroxylation to its active form prednisolone,[6] but the rate of hydroxylation is affected by liver disease and shows individual variation.[7] Prednisone is not only less reliable but also more expensive in Britain than prednisolone.

Dexamethasone and betamethasone are very potent, are devoid of mineralocorticoid activity, and have very long biological half lives (36-54 hours). Hydrocortisone is 75% bound to cortisol binding globulin (transcortin),[8] but less than 1% of the plasma concentration of dexamethasone or betamethasone is bound in this way.[5] These steroids are, therefore, more active and their duration of action is more prolonged—with the associated increased risk of severe side effects, which rules out their use.

Corticotrophin given intramuscularly as a depot formulation two or three times a week may be used in chronic asthmatics and may increase production of hydrocortisone by as much as fourfold. This line of treatment has several drawbacks, however, the most important being the unpredictable response of the adrenal cortex to stimulation. Corticotrophin stimulates production of mineralocorticoids and hydrocortisone and so increases any tendency to fluid retention. The secretion of corticotrophin releasing factor from the hypothalamus is suppressed. Severe allergic reactions to corticotrophin have been reported.[9,10] Bruising is more common than with other synthetic corticosteroids. These disadvantages outweigh any advantages even in children, in whom a growth sparing effect has been claimed —but the claim is open to discussion.[11]

The long acting intramuscular preparation triamcinolone acetonide given as 80 mg once a month has been used in chronic asthmatics with some symptomatic success.[12-14] It appears, however, to be excessively potent; work in rats suggests that its anti-inflammatory potency is 10 to 15 times greater than that of triamcinolone acetate or prednisolone,[15] a fact not always appreciated.[16] This high potency is probably why triamcinolone acetonide causes excessive adrenal suppression, proximal myopathy, bruising, and hirsutism; and not surprisingly it improves the control of asthma when compared with prednisolone in a non-equipotent dosage.[13,14,17] One group that has used the drug has now noted its excessive toxicity and states that it should not be used to treat chronic asthmatics, a viewpoint that we strongly support.[18]

What, then, is the most suitable steroid for oral use? The answer is prednisolone with its plasma half life of two to three hours and biological half life of 18 to 36 hours[4,5] and high affinity for binding to transcortin.[19] The side effects of adrenal suppression may be minimised by giving the steroid in the early morning as a single daily dose; at this time endogenous cortisol is at its peak, which reduces negative feedback effect on the hypothalamic-pituitary-adrenal axis. The diurnal variation of transcortin binding affinity is at its lowest in the morning, allowing more free steroid to be active if given at this time, while during the day the binding increases, reducing the free concentration of the drug as the day progresses, thus minimising excessively prolonged high concentrations.

Some workers suggest that alternate day single morning dosing with prednisolone reduces side effects even further.[20] Unfortunately, the control of asthma may be less effective on the non-steroid day,[21] though this appears to be less of a problem in children.[11] Early morning once daily administration of prednisolone in adults, and on alternate days in children, appears to be the optimal drug regimen for maintenance treatment with systemic corticosteroids in patients with chronic severe asthma.

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Electrophysiological testing after acute myocardial infarction

The long term prognosis in patients surviving acute myocardial infarction depends mainly on the extent of myocardial damage, the residual left ventricular function, the presence and progression of additional coronary artery disease, and the degree of ventricular electrical instability.[1-4] Attempts to measure the risk need to consider these multiple factors in order to identify the high risk groups, who need treatment, and the low risk groups, who do not. The contribution of exercise testing after myocardial infarction—which identifies inducible ischaemia secondary to occult coronary artery disease—has been extensively investigated and will not be discussed here.[5-6]

Many of the patients who die after an infarction do so suddenly without evidence of reinfarction.[7] This observation has led to sustained interest in the identification of markers of ventricular electrical instability. A correlation exists between complex ventricular extrasystolic activity (as shown by ambulatory electrocardiographic recording) and the degree of impairment of left ventricular function,[8] though the two factors are of independent prognostic importance.[3 9] The risk of sudden death is increased in patients with frequent ventricular extrasystoles, particularly complex forms,[3 4 9] or runs of non-sustained ventricular tachycardia.[10] Treatment with antiarrhythmic drugs had been assumed to improve the prognosis of these patients, but the results of trials based on high risk groups have been disappointing despite a substantial reduction in ventricular extrasystolic activity.[11 12] Several explanations have been advanced for this apparent paradox. The reduction in extrasystoles might not reflect the ability of the drug to prevent sustained ventricular tachycardia or fibrillation, and the designs of the studies did not allow for the increasingly recognised proarrhythmic effect of class I antiarrhythmic drugs in some patients.[13]

These difficulties have stimulated interest in a more direct approach to assessing electrical instability after myocardial infarction using techniques of programmed ventricular stimulation initially evolved for patients with chronic recurrent ventricular tachycardia.[14] In such cases one or more temporary pacing electrodes are inserted for intracardiac stimulation and recording and an attempt is then made to initiate the tachycardia by introducing single, double, or sometimes triple ventricular extrastimuli during sinus rhythm and ventricular pacing. Most of the tachycardias induced may be terminated by overdrive pacing, but in about one fifth of cases cardioversion is necessary.[14] Once a tachycardia has been shown to be inducible the patient may be given an antiarrhythmic drug and another attempt made to induce the tachycardia. Several drugs may need to be tested in this way. Clearly this approach provides direct evidence that a given drug prevents the initiation of tachycardia and identifies unwanted proarrhythmic effects,[15] and treatment based on the findings has been associated with a reduction in recurrence of tachycardia and an improvement in prognosis.[16]

Initial studies using the results of programmed ventricular stimulation as a prognostic index in patients after myocardial infarction have given conflicting results.[17-19] Some of the variability in results is attributable to the small numbers studied, the selection of patients, and differences in electrophysiological technique. The induction of as few as two consecutive ventricular beats appeared to identify a group at high risk of sudden death in one study,[17] while in another report the results of programmed stimulation—even including the initiation of sustained ventricular tachycardia—appeared to provide no prognostic information whatsoever.[19] A similar lack of predictive value was reported in a series of 267 patients with coronary artery disease who were tested during routine arteriography.[20]

Denniss and his coworkers from Sidney have recently published a study in which they assessed both electrical instability and inducible ischaemia as determinants of survival after recent infarction.[21] From a total of 375 consecutive survivors of acute myocardial infarction, 111 patients were excluded for reasons including recurrent angina, uncontrolled heart failure, late ventricular tachyarrhythmias, and age. These exclusions are important: the one year mortality in the excluded patients was 22% compared with 10% in the study group. The remaining 228 patients were investigated by programmed ventricular stimulation and treadmill exercise testing, though both procedures were undertaken in only 138 patients. Treatment with antiarrhythmic drugs was not given on the basis of the results of programmed stimulation but only for spontaneous arrhythmias. Electrical instability was shown in 38 patients and their one year mortality was 26% compared with 6% in the remainder. The combination of negative results from the electrophysiological and exercise