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Reprinted from

THE LANCET

Vol 338 LONDON SATURDAY 10 AUGUST 1991 No 8763

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Telepharmacodynamics to predict therapeutic effects of glucocorticoids

SIR,—Dr Brown and colleagues' report (March 9, p 576) prompts us to propose a new clinicopharmacological concept for glucocorticoid therapy. Glucocorticoids have various pharmacological effects on many different organs, and in chronic diseases it is difficult to predict individual sensitivity to glucocorticoids unless the patient is recovering satisfactorily. A pharmacokinetic approach has not been successful.[1] The resulting overdosing or underdosing can produce side-effects or lead to disease recurrence and the adverse consequences of prolonged therapy.[2]

The adverse effects of glucocorticoids seem to be more frequent in patients whose peripheral blood lymphocytes show impaired susceptibility to the agent[3] and favourable clinical effects tend to be seen in patients whose lymphocytes are sensitive.[4] Thus glucocorticoid-sensitive patients can be discriminated from resistant patients by in-vitro lymphocyte proliferation tests. Unfortunately, these tests are tedious and time-consuming. To overcome these difficulties, a "pharmacological telescope" may be helpful. This permits the pharmacodynamics or therapeutic efficacy of glucocorticoids to be viewed via effects on remote cells on which glucocorticoids produce easily observable pharmacological changes.

The first example is the glucocorticoid effect on the hypothalamic-pituitary-adrenal axis, resulting in a decrease in circulating cortisol. This reflects the action of steroids on the immune system.[5] In our study half the patients with chronic renal failure were steroid resistant—and they showed acute allograft rejection while under high-dose glucocorticoid immunosuppression.[6] The second example is the cutaneous vasoconstriction response in asthma presented by Brown et al. Glucocorticoid resistance tended to be found in steroid-resistant asthmatic patients treated with 20–40 mg prednisolone daily. Measurement of peripheral blood concentrations of endogenous cortisol in the kidney recipients and the study of the intensity of forearm skin blanching in the asthmatic patients both proved to be useful telescopes for discrimination between glucocorticoid sensitive and resistant patients.

Suppression of endogenous cortisol concentration and peripheral vasoconstriction are well-known effects of systemic and topical glucocorticoids, respectively. The pharmacological mechanism of these effects and of therapeutic immunosuppression have been thought of as independent of each other. Moreover, glucocorticoid effects on the hypothalamic-pituitary-adrenal axis are seen only as unfavourable, and we cannot be certain that the greater the hormonal suppression, the greater the immunosuppression. Whether or not the different pharmacological effects are indeed independent (could there be some relation between cell susceptibilities toward glucocorticoids via a common receptor/steroid interaction?) the two examples do suggest that the action of glucocorticoids upon different organs, such as the hormonal network and vascular smooth muscle, predicts effects on target organs such as the immune system and bronchial smooth muscle. This concept may be referred to as glucocorticoid "telepharmacodynamics".

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