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COMPARISON OF CLOPREDNOL AND PREDNISOLONE IN CHRONIC ASTHMATIC PATIENTS

Determination of the time course of response in patients with chronic bronchial asthma indicated that following a single oral dose of 40 mg prednisolone, a maximum effect was detected after 9 h, which was similar to the same dose of prednisolone given intravenously (maximum effect 8 h). Intravenous hydrocortisone, however, produced a much earlier peak effect at around 5 h (Ellul-Micallef, 1972; Ellul-Micallef, Borthwick & McHardy, 1974; Ellul-Micallef & Fenech, 1975). Cloprednol (6-chloro-11 β ,17 α , 21-trihydroxypregn-1 6 triene-3, 20 dione) is a new synthetic glucocorticoid (Figure 1). It has a relative anti-

Figure 1 Structure of cloprednol.

inflammatory potency approximately twice that of prednisolone (Ortega, Rodriquez, Strand, Bessler & Segre, 1976; Buisseret & Parrott, 1978). Its plasma half-life in man is around 90–100 min, similar to that of hydrocortisone (Collins, Clark, Harris & Townsend, 1970), whereas the reported half-life of prednisolone is about 240 min (Peterson, 1959). It was, therefore, thought that the peak effect of response to oral cloprednol might approximate more to intravenous hydrocortisone than to oral or intravenous prednisolone. The present study was designed to test this hypothesis.

Twelve patients aged between 17 and 51 years, diagnosed clinically as suffering from chronic bronchial asthma participated in the study. Informed consent was obtained from all the patients. Individual patient data are summarized in Table 1. In none of the patients had corticosteroids been used previously and during the study they received no drugs other than the ones under test. No patient had taken barbiturates or other enzyme-inducing agents prior to the study. ECGs, renal and hepatic function tests were all normal. Apart from some hyperinflation all chest X-rays were normal and there was no evidence of respiratory infection in any case. On days 1, 3 and 4 the patients received placebo capsules under single blind conditions, whilst the active drugs were randomly administered on days 2 and 5 under 'double-blind' conditions. The stability of the patients' clinical state was determined during day 1 whilst

Figure 2 Effect of a single oral dose of 40 mg prednisolone (●) or 20 mg clobprednol (○) on peak expiratory flow rate. Group mean values $\pm$ s.e. mean are shown for twelve patients. *Values at 1 and 2 h were not significantly different from control ($P < 0.05$).

placebo was administered during days 3 and 4 in an attempt to eliminate any carry over effect.

Identical gelatin capsules containing 2.5 mg clobprednol or 5 mg prednisolone were prepared. Placebo capsules identical in taste and appearance contained only starch and lactose. Single doses of drug only were used, 20 mg clobprednol and 40 mg prednisolone. All treatments were administered at 08.00 h.

Pulmonary function measurements consisted of three repeated recordings of peak expiratory flow rate over a 3 min period using an Air-Med peak flow gauge. The best of the three successive attempts was chosen and recorded. The procedure was repeated at hourly intervals for 12 h following drug administration. Previous experimental work indicated that PEFR is as reliable an index of change as dynamic and static lung volumes, thoracic gas volume, airway resistance

Table 1 Clinical and physiological data of patients studied

Number	Sex	Age (years)	Eosinophilia	Intradermal tests*	Duration of asthma (years)	Immediate pre-clobprednol PEFR (l/min)	Immediate pre-prednisolone PEFR (l/min)
1	F	40	0	0	5	220	210
2	M	24	Blood and sputum	+	16	300	260
3	M	21	Blood	+	7	300	270
4	M	34	Blood	+	34	320	370
5	M	32	Blood	+	24	230	190
6	F	26	Blood	+	20	220	210
7	M	43	0	0	2	280	300
8	M	51	0	+	41	220	210
9	M	44	0	0	3	200	190
10	M	51	0	0	4	270	280
11	F	17	Blood	+	13	250	290
12	M	35	Blood	+	29	310	320

* + = Positive to a wide variety of antigens.

and maximum expiratory flow-volume curves (Ellul-Micallef *et al.*, 1974).

There were no significant differences in status between the group to which cloprednol was first administered and that which received prednisolone initially. No significant diurnal variation was observed nor could any response to the placebo capsules be demonstrated within either individuals or the group as a whole. The PEFR values obtained during the placebo days were not significantly different from the immediate pre-treatment values recorded on days 2 and 5. The results obtained following the treatment with either cloprednol or prednisolone have, therefore, been compared with those measurements recorded immediately before drug administration. In order to reduce the effect of individual variation all measurements have been expressed as a percentage of the pre-treatment value.

Of the twelve patients, patients nos. 4 and 8 showed no response to either drug. Both cloprednol and prednisolone produced consistent changes in PEFR in all the other ten patients. Figure 2 shows the time course of response to prednisolone and cloprednol for the twelve asthmatic patients. The peak effect occurred at 9 h following prednisolone administration and 7 h after cloprednol had been given. Changes in PEFR were statistically significant from the third hour onward after both cloprednol and prednisolone administration ($P < 0.02$, for the third hour, $P < 0.001$ for values obtained from the fourth to twelfth hour). Individual peaks following cloprednol ranged from 7 to 10 h, whilst in the case of prednisolone, these ranged from 8 to 11 h. Although the plasma half-life of cloprednol is similar to that of hydrocortisone, its time course of action in chronic bronchial asthmatics

was not found to be the same. There was no statistical evidence of a difference between the peak effect of response (mean $\pm$ s.e. mean) in PEFR to 20 mg oral cloprednol ($171\% \pm 12\%$) and such a response to 40 mg oral prednisolone ($177\% \pm 13\%$), thus supporting the approximate 2:1 potency ratio of cloprednol to prednisolone on a mg for mg basis. However, in most patients there did seem to be a trend to reach a peak response 1–2 h sooner when cloprednol was administered. In the case of both drugs a statistically significant improvement in PEFR occurred only after 3 h so the onset of response was similar. Neither drug seemed to produce any significant change after 30 h.

In 1698, Sir John Floyer, himself an asthmatic, published the first edition of his book, *A Treatise of the Asthma*. One of his many relevant observations states that: 'The asthma is a long disease and it required a long observation to give a true account of its symptoms, changes and various causes, which common patients cannot nicely observe'. His maxim is certainly worth bearing in mind especially when one is evaluating a drug for the treatment of this condition.

R. ELLUL-MICALLEF & F.F. FENECH

Departments of Physiology and Medicine, University of Malta, Malta

D. PARROTT

Institute of Clinical Medicine, Palo Alto, California, USA

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