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Report No. W – 5615

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Internal Research Report

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(compiled by Dr S W Holmes)

Department: Pharmacology

Date: 13 January 1982

Title: General pharmacological and drug interaction studies with Ro 0--3780 (13-cis retinoic acid) administered orally.

Summary: (continued on next page if necessary)

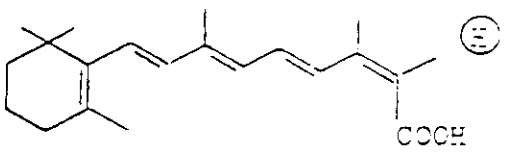
See page 5

NB: See next page for Ro-numbers and structural formulae of all compounds discussed in Screening Reports only those compounds which are commented upon therein numbers and signatures

Ro-numbers*):

04-3780

Theme numbers: 3335



The work reported here was carried out by the following workers:

Unanaesthetised cat study

Dr L C Blaber (Study Supervisor), Mr D T Burden and Miss Y Burke.

Immunopharmacology

Dr A J Kennedy (Study Supervisor), Mrs J Hawkes and Miss S Jones.

Interaction with dexamethasone

Mr C H Cashin (Study Supervisor), Mrs V Gibson and Mr E J Lewis.

All other studies

Dr S W Holmes (Study Supervisor), Mr D Coles, Mrs C Ellis, Miss J Monk and Mr K Wilson.

The overall Study Director was Dr S W Holmes.

*) Ro-numbers of all compounds discussed (in Screening Reports only those compounds commented upon)

DECLARATION

I, the undersigned, hereby declare that this work was performed under my direction during November and December 1981 according to the procedures herein described and that this report represents a true and accurate record of the results obtained. The original experimental data upon which this report is written are stored in the department archives under the control of the Pharmacology Department GLP Co-ordinator.

Simon W Holmes, BSc, PhD
Study Director.
14 January 1982

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Ro 04-3780 (13-cis retinoic acid) has been shown to be of value in the oral treatment of severe acne and it is proposed to file a product licence application for this indication with the UK regulatory authorities. Examination of the available data revealed major deficiencies in the animal pharmacology necessary to support such an application.

This report will give results on general pharmacological and drug interaction studies with orally administered Ro 04-3780. It is proposed that the clinical dose of Ro 04-3780 will be in the range 0.1 to 1 $mg.kg^{-1}$ for up to 4 months although doses up to 3 $mg.kg^{-1}$ have been used in the USA. Therefore it was decided to use a dose of 30 $mg.kg^{-1}$ p.o. administered daily for 10 days in our animal general pharmacology studies.

A summary of the results reported here is given in Tables 1 and 2. No pharmacological effect or drug interaction of Ro 04-3780 was detected in laboratory animals which would contra-indicate the compound's administration to man.

1.2.1 Central Nervous System

(a) MOUSE

Effect on gross behaviour

Groups of 6 male MF1 mice (18 - 22g) received Ro 04-3780 300 mg.kg^{-1}, or vehicle orally each day for 10 days. The animals were observed 0.5, 1, 3, 6 and 24 hr after the first dose, 1 hr after dosing on days 2 to 9 and 1, 3, 6 and 24 hr after dosing on day 10. Animal observation was carried out to determine behavioural effects using a check list (Figure 1) based on that of Irwin (Psychopharmacologia, 1968, 13, 222). Rectal temperature was recorded at each observation and body weight was determined daily at the time of dosing.

Although daily administration of Ro 04-3780, 30 mg.kg^{-1} p.o., for 10 days did not have a pronounced effect on gross behaviour certain evidence of CNS stimulation and muscle relaxation was seen during the study. These effects are summarised in Table 3. Table 4 gives the effect of vehicle and drug on rectal temperature throughout the study; on days 2, 4 and 7 and 24 hr after the tenth dose Ro 04-3780 caused a significant elevation of rectal temperature which was probably associated with the mild stimulant effects of the drug observed. Body weight gain from day 1 to 10 was not significantly different between Ro 04-3780 treated (5.8 ± 0.5 g) and vehicle treated (5.0 ± 0.9 g) animals.

It is concluded that, apart from a marginal CNS stimulation, Ro 04-3780 did not have gross behavioural effects in the mouse.

Laboratory book reference: SF-20

Figure 2 [illegible]

Drug: .... Route: .... Date: ....

Dose: .... Observation times: .... Investigator: ....

Observation	Normal Score	Max. Effect	1	2	3	4	5	6	Total
CNS Depression:									[illegible]
Spontaneous activity	2	0							
[illegible]	2	0							
Reactivity	4	0							
Pain Response	2	0							
Startle Response	2	0							
[illegible] retraction	2	0							
Total									
CNS Stimulation:									[illegible]
Irritability	2	4							
Hyperactivity	2	4							
Increased startle	2	4							
Increased touch	2	4							
Piloerection	0	2							
Exophthalmos	0	2							
Tremors	0	2							
Convulsions: C.T or CLT	0	2							
Total									
Muscle Relaxation:									[illegible]
Low limb posture	2	0							
Abdominal tone	2	0							
Limb tone	2	0							
Grip strength	2	0							
Ataxia	2	0							
Inclined screen	2	0							
Total									
Reflex Depression:									[illegible]
Placing	2	0							
Ipsilateral flexion	2	0							
Righting	2	0							
Total									
Other Effects: Score normal (0), increased (+) and decreased (-)									
Skin colour									
Respiration									
Salivation, P or V									
Lacrimation									
Diarrhoea									
Rectal Temperature °C									

Other effects and general comments: ....
....
....
....
....

Table 3

Gross behavioural effects

Day of treatment	Time of observation post-dose (hr)	Behavioural effects
1	0.5	Reduced grip strength 1/6.
	1	Reduced spont. activity 3/6, increased touch response 2/6, piloerection 2/6.
	3	Increased irritability 2/6, increased touch response 1/6.
	6	Increased irritability 1/6, increased touch response 2/6.
	24	Increased irritability 1/6, hyperactivity 1/6, increased touch response 2/6.
2 - 9	1	Instances each day of some of the following: increased irritability, increased touch response, hyperactivity, reduced grip strength, reduced abdominal tone.
10	1	Increased irritability 1/6, hyperactivity 3/6, increased touch response 2/6, reduced abdominal tone 1/6.
	3, 6 & 24	Marginal evidence of CNS stimulation never reaching a significant score (52, 54 and 53 respectively).

D GENERAL DISCUSSION AND CONCLUSIONS

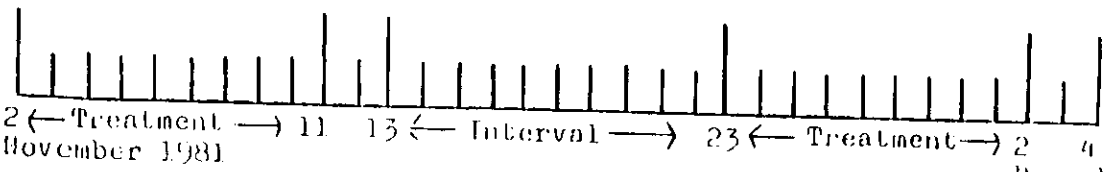
The only effects noted for Ro 04-3780 in this work were a marginal behavioural stimulation and immunosuppressive activity in one test in mice, an effect which was reflected in the adjuvant arthritis test in rats. There was also the suggestion that Ro 04-3780 treatment may render cats more sensitive to infection; this last observation would be consistent with an immunosuppressant activity. Therefore the only effects noted could be associated with the immune response and there is ample evidence in the literature that retinoids including Ro 04-3780 are capable of specific modulation of this response and, indeed, such activity may be a necessary part of Ro 04-3780's activity against acne.

No evidence of interaction with drugs liable to be co-administered with Ro 04-3780 was obtained.

It is concluded that no pharmacological effect or drug interaction of Ro 04-3780 was detected in laboratory animals which would contra-indicate its administration to man.

Appendix I
(see page 18)

Protocol for experiment to test the effect of Ro 04-3780/016 in conscious cats



2 Male I_{35} K_{35}
Dosed with 80 mg/day Ro 04-3780/016
2 Female E_{35} G_{35}

2 Male H_{35} J_{35}
Dosed with 4 placebo capsules/day
2 Female D_{35} F_{35}

recording out to time of placebo administration

I_{35} K_{35}
Dosed with 4 placebo capsules/day
E_{35} G_{35}

H_{35} J_{35}
Dosed with 80 mg/day Ro 04-3780/016
D_{35} F_{35}

recording out to time of placebo administration

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