(Bradshaw *et al.*, 1979); a dopamine agonistic action, which could account for the delay in emptying (Lanfranchi *et al.*, 1978; Proctor *et al.*, 1981), was never observed in several *in vivo* and *in vitro* experiments performed in our laboratory (Bertaccini, unpublished observations).

The action of ranitidine seems to be independent of H₂-receptor blockade (with consequent inhibition of gastric secretion) as shown by the inactivity of cimetidine. The same data allowed us to exclude effects related to changes in intraduodenal pH (Cooke, 1975). However an influence of changes in plasma gastrin levels cannot be excluded on the basis of our experiments. Thus a non-specific effect of the molecule rather than an effect connected with the H₂-receptor blockade must be hypothesized. Species differences may be responsible for the opposite effect observed in man (delay of gastric emptying) and in rat (acceleration of gastric emptying). The different route of administration with possible changes in bio-availability must be considered. Moreover, Parsons (personal communication) observed poor, irregular absorption of H₂-antagonists after intraperitoneal administration in the rat. However, the differences in the activity of the various H₂-receptor blockers

observed both in rat and in man are consistent with the idea that H₂-receptors are not involved in the control of gastric emptying, at least in these two species.

The effect of ranitidine was observed after intravenous injection with consequent high blood levels of the compound; if the effect on gastric emptying is confirmed also after repeated oral administrations, ranitidine could represent a useful agent for the treatment of ulcer patients with deranged (increased) gastric motility. However, according to the only preliminary report on this topic (Mignon *et al.*, 1980), single oral administration of ranitidine does not change gastric emptying rate in man.

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SIX MONTHS EXPERIENCE OF NEW PROCEDURES AFFECTING THE CONDUCT OF CLINICAL TRIALS IN THE UNITED KINGDOM

Details of the new procedures affecting clinical trials in the United Kingdom have been given previously (Griffin & Long, 1981; Griffin & Diggle, 1981). In a recent editorial in this journal by Binns (1981) interest was expressed in the effect such changes would have on the testing of new chemical entities

(NCE) in the United Kingdom in the light of earlier statements that an overwhelming majority of early clinical trials of drug molecules originating within the British Pharmaceutical Industry were being conducted overseas (Cromie, 1980).

In Table 1 are shown details of the one hundred and

Table 1 Clinical trial exemptions (CTX) received by the UK licensing authority in the first six months of operation of the scheme

Nature of applicant company	Clinical trial exemptions (CTX)							
	March-June 1981				July-September 1981			
	Total CTX application	New chemical entities	New salt or ester	New route	Total CTX applications	New chemical entities	New salt or ester	New route
British owned	3	1	0	0	10	4	0	7
Foreign owned with UK research facility	24	6	1	1	31	5	0	1
US owned	6	1	0	0	9	2	0	0
EEC owned	9	2	1	0	24	3	2	1
European non EEC	2	0	0	0	8	0	0	0
Other	1	0	0	0	2	1	0	0
Total	48	10	2	1	84	15	2	9
Applications not determined in 35 days and requiring 28 days extension	3				6			
Application incomplete	0				1			
CTX refused	0				2			

thirty-two applications from pharmaceutical companies for exemption from the need to hold a clinical trial certificate (CTX) in accordance with the procedures laid down (Statutory Instrument 1981 No 164), and involved applications to evaluate twenty-five NCEs and four new salts or esters. Ten CTX applications also involved programmes to evaluate existing chemical entities by a new route of administration to man. In only nine of these one hundred and thirty-two applications was it necessary to extend the thirty-five day period for processing these CTX applications for a further twenty-eight days. Only two applications have been refused, although seventeen have been referred back to the applicant for modification of the clinical trial programme before the clinical trial exemption was permitted.

The figure of twenty-five NCEs received and granted permission to undergo clinical evaluation under the exemption scheme over the first six months of its operation (March–September 1981) compares favourably with those received for the previous two years. Forty-one NCEs out of a total of one hundred and seven clinical trial certificates (CTC) granted in 1979, thirty-four NCEs out of a total of eighty-seven CTC applications granted in 1980.

The processing times for these one hundred and thirty-two CTX applications were within the thirty-five days indicated in 'The Medicines (Exemption from Licences) (Clinical Trials) Order 1981' (SI 1981 No 164) except for nine cases where the provision to extend the period by a further twenty-eight days was invoked. This compares well with the delay time to process CTC applications which averaged two hundred and two days for all CTC applications and two hundred and fifty-one days for NCEs in 1979, and two hundred and thirty-one and two hundred and eighty-seven days respectively in 1980.

Clinical trial certificates are issued initially for two years and may be renewed on a two yearly basis. Of ninety-nine CTCs granted and still current in 1979, thirty-three were for NCEs, of eighty-six in 1980, twenty-one were for NCEs and of thirty-one in the first nine months of 1981, four NCEs are still on trial.

Another objective of the new scheme is to permit rapid extension of the programme as more information on the safety and efficacy of the product becomes available. This extension is by request to increase the scope of the initial CTX. In the first six months there have been twenty-two with one extension; nine with two extensions; three with three, one with four and one with five extensions.

Since the inception of the new exemption scheme, there has been almost a complete switch by manufacturers from the system applying for clinical trial certificates to use the new procedure. There has also been a significant reduction in the number of applications from doctors and dentists to be exempt from the need to hold a clinical trial certificate (CTE) which

permits them to initiate and conduct on their own responsibility The Medicines (Exemptions from Licences) (Special Cases and Miscellaneous Provisions) Order 1972 (SI 1972 No 1200). In 1979 and 1980 there were three hundred and fifty-six and three hundred and twenty CTEs respectively, i.e. about eighty per three month period. In the first quarter of 1981 there were eighty-two CTEs but since the introduction of the new procedure the applications for CTEs fell to forty-eight and fifty-one in the second and third quarters respectively.

In summary, therefore, it would appear that the

changes introduced have resulted in speeding up the process which permits clinical trials on new chemical entities to be initiated and, over a six month period, the number of new chemical entities being brought to trial is greater than in any six month period in the past two years.

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ARE PROPRANOLOL AND NIFEDIPINE SYNERGISTIC IN ANGINA PECTORIS?

Dr Tweddel and her colleagues (Tweddel *et al.*, 1981), in their study of the efficacy of the combination of propranolol and nifedipine in angina pectoris, have shown that nifedipine confers additional benefit when added to propranolol monotherapy. However, their claim to have demonstrated a synergistic effect of the combination is completely vitiated by their failure to assess the efficacy of nifedipine given alone. The more so, indeed, since a reduction in the dose of propranolol maintained the anti-anginal effect whilst actually increasing exercise tolerance and maximum oxygen consumption. It is rather unusual for a synergistic effect to be enhanced by a reduction in dosage of one of the agents, although, clearly doses have to be chosen which will, as far as possible, minimize toxicity.

That is not to deny the possibility of synergism of these drugs, and the open study of Oakley *et al.* (1979) would be consistent with it. Nevertheless, the enhanced effect obtained by reduction in propranolol

dosage could as readily be interpreted as suggesting that propranolol attenuates the effect of nifedipine rather than exhibiting synergism with it. Hence the difficulty created by the absence of a period of nifedipine monotherapy in their protocol. Furthermore, it might have been interesting to have seen the result of using half-dose propranolol alone, especially in patients with compromised left ventricular function.

It is not legitimate to claim the existence of synergism in a drug combination without adequate (or in this case any) characterization of the effects of the exhibition, in optimum dosage, of both individual agents.

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