EVIDENCE FOR SAFETY OF NEW DRUGS

Lemberger, Terman, Rowe & Billings (1976) reported in this Journal on a new potential antidepressant, nisoxetine. They demonstrated clearly that it, like the established antidepressants, greatly increases the response of the blood pressure to noradrenaline.

They stress its safety: 'We conclude that nisoxetine, in safe doses, specifically etc.'; 'Thus, nisoxetine appears to be a safe agent which is well tolerated at doses which should be clinically effective'; 'Nisoxetine appears to be safe and well tolerated at doses at which it produces this effect ...'. They base these statements on their experience with nine normal volunteers who each took the drug for 8 days.

The study was a perfectly reasonable one and seems to have been competently done. However, there is no way that data from nine normal volunteers taking a new drug for 8 days can be interpreted as indicating that the drug itself is safe or that the doses used are safe. Such claims are not really in the interests of the drug, the pharmaceutical firm concerned, or the Journal.

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SOME CLINICAL PHARMACOLOGICAL STUDIES WITH BUTRIPTYLINE, AN ANTIDEPRESSIVE DRUG

Butriptyline hydrochloride is a tricyclic compound chemically related to amitriptyline and imipramine and claimed to possess antidepressive activity (Grivois, 1971; Kapadia & Smith, 1976). Pharmacological studies in animals have demonstrated anticholinergic activity with antagonism of the central and peripheral effects of tremorine (Herr, Voith & Jaramillo, 1971) and of the arousal reaction induced by physostigmine (Jaramillo & Greenberg, 1975). Like imipramine and amitriptyline, it reverses reserpine-induced hypothermia and prolongs the amphetamine-induced hyperthermic response (Herr et al., 1971), but unlike these compounds, it does not potentiate the action of noradrenaline on the nictitating membrane or antagonize the action of guanethidine on the vas deferens (Jaramillo & Greenberg, 1975) nor does it influence the accumulation or metabolism of intraventricularly injected noradrenaline in areas of rat brain (Pugsley & Lippmann, 1974). This indicates that it has little, if any, inhibitory action on the neuronal uptake of catecholamines. An investigation has, therefore, been carried out into the influence in healthy volunteers, of single and repeated doses of butriptyline on the tyramine pressor response, a convenient model of catecholamine reuptake, and on parasympathetic activity.

Ten healthy volunteers (seven female, three male) aged 20-55 years were studied, having been drug free for at least one week. In six female subjects, single dose studies were carried out in which each received in random order based on two latin square designs, under double-blind conditions, either butriptyline (50 mg) or identical placebo using the double dummy technique. Anticholinergic tests were carried out at 2.5 and 4 h, and a tyramine pressor response at 3 h, after administration of the treatments. At least 1 week elapsed between consecutive treatments. The other four subjects (three male, one female) took part in a repeated dose study in which butriptyline (25 mg 8 hourly) or identical placebo was administered for 5 days, the test procedures being carried out 2 h after the morning dose on the fifth day. Each subject received both treatments in a balanced cross-over design with at least 1 week elapsing between treatment periods. In both studies, blood was taken just before and after the tyramine pressor response tests for estimation of plasma butriptyline and norbutriptyline.

The tyramine pressor response was measured as described by Ghose, Turner & Coppen (1975). Blood pressure was measured with a mercury sphygmomanometer following intravenous in-