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COMMENTS ON STUDY 50/70-1

Double blind crossover study to assess the effects of sertraline on psychomotor performance and interaction with diazepam

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U.K.

This study was stopped prematurely due to side effects. After taking even the first dose (150mg of active drug) all volunteers began to complain of side effects. These continued either unabated or with increased severity till the 4th day of dosing when the study was stopped. The subjects were healthy females aged between 27 and 42. They are experienced volunteers in such studies and could be considered well motivated to adhere to study procedures.

Interview with the subjects revealed that 5 out of 5 subjects receiving sertraline had severe side effects and only one out of 7 placebo subjects complained of minor side effects. The sertraline subjects first complained of a fullness in the stomach/nausea within 4-5 hours of first dose. This was associated with anorexia and a feeling of general malaise. The symptomatology progressed such that by 8-12 hours after dosing subjects began to complain of severe frontal headache (resembling migraine in those subjects who had a migraine in their younger years). Insomnia was profound in that the volunteers could not get to sleep, some eventually only sleeping for 2-3 hours from about 4.00 a.m. On rising the following day they did not feel drowsy or weak. Comments such as "I was running like a machine inside" and "I have never felt as bad as this in my life" were made.

Several subjects spontaneously remarked that their vision was blurred, associated, in one volunteer, with marked mydriasis. One further disturbing symptom was of choking/incoordination of the motor muscles of jaw and oro-pharynx. On discontinuing medication it took 1-3 days for the symptoms to subside.

Impression

I consider this to be reliable information from these volunteers and also the symptoms to be drug related. There was no question of the volunteers conferring on the nature of their side effects as the reports were all telephoned to the study coordinator independently. These side effects have been noted previously with sertraline and other serotonin specific antidepressants. However, the severity of

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symptomatology in these cases is disturbing. There is no possibility of drug interaction and I believe we have an example of susceptibility to drug.

The pattern of side effects suggests that sertraline is an amphetamine like stimulant and it is possible that we are seeing an interaction between serotonergic and dopaminergic functions, cf. the motor incoordination. However, interference with GABA transmission has not been ruled out. It may well be that these symptoms are due to the disturbance of an intact physiological system by a potent serotonergic agent, thereby accounting for the lack of untoward effects observed in depressed patients. However, healthy volunteers have received up to 400mg for 14 days without severe untoward reaction and therefore these women may be considered possibly hypersensitive. The question of an error in capsule dosage must be considered also.

Actions

(1) Assay serum for levels of parent compound and metabolite.

(2) Analyse capsules for sertraline dosage.

(3) Make full study report when data is in house.

Declan Doogan

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