F. Leeters

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Dear Skitch,

I was pleased to review the data for the compound Si 93. The volume consisted of three parts: pharmacology and toxicology, dated 19 August 1970; clinical pilot studies dated November 2, 1972; and psychometric studies dated June 17, 1974.

The pharmacologic evidence indicates that Si 93 is atropine-like with tachycardia, mydriasis, and dry mouth as predominant symptoms. It is readily absorbed and at high doses inhibits gastric secretion. The anticholinergic actibity was also manifest in EEG studies in rabbits and cats where Si 93 exhibited atropine-like patterns. The anticholinergic activity suggested its use as a spasmolytic.

In the clinical studies, the dose range is defined. At 5 mg, there were no effects. At 40 mg, anticholinergic and sedation occurred. At 60 mg, the subjects complained of fatigue and drowsiness in addition to the anticholinergic effects. In a crossover controlled study of 25 mg and 50 mg Si 93, the differences between the two doses were small with greater changes in pulse rate for the 25 mg dose.

The psychometric test data reports interesting findings. Eight volunteers were seen in a double-blind crossover study of Si 93 and 25 mg and 50 mg, oxazepam 20 mg, as a comparison substance, and placebo. The 50 mg dose of Si 93 elicited greater sedation than 20 mg oxazepam, but also an inner "stimulation", irritability, unpleasantness, feelings of warmth, and some clouding of sensorium. The 25 mg doses of Si 93 was found to be pleasant and equivalent to 20 mg oxazepam.

These observations strongly suggest that Si 93 has central activity at the doses studied; that the activity is pleasant and 'tranquillizing' at low doses, but unpleasant at high; that there is a relatively narrow therapeutic range, for the 50 mg dose elicits some of the central deliriant effects of the anticholinergics. There are some interesting questions about the compound:

Are the central effects similar to oxazepam (and other benzodiazepines), or like imipramine (ditran, and other thymoleptics)?

Does Si 93 have a diphasic effect--sedative and pleasant at lower doses, and stimulant and deliriant at higher doses?

These questions can be answered by our present methods of electrophysiologic assay, for a classification study will define the type of central activity in man and yield evidence of its therapeutic range; and a dose-ranging study will give data for the stability or the nature of the central effects.

However, the questions that must be answered by management before these studies are undertaken seem to me to be: Is there a need for a novel thymoleptic; and if there is, can Si 93 qualify for further study since it may have a narrow therapeutic range?

If the answer is affirmative and further studies are desired, we would be pleased to examine this compound. For a dose-finding study, single doses of 5,10,20, 40 and 60 mg should be examined. For a classification study, two doses and placebo could be examined in 10-12 subjects over a post-drug four hour period with measurement of EEG, alertness, heart rate, blood pressure, mood ratings, symptom ratings, and critical flicker fusion (CFF), and the observations compared with our historical standards diazepam and imipramine.

It seems to be an interesting centrally active compound. Again, my thanks for the opportunity to review these data in their German originals.

My best regards.

Sincerely yours,

Max Fink, M. D.
Professor of Psychiatry

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