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Studies on Cross Tolerance with LSD-25, UML-491 and JB-336

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Recent researches raise the problem whether cross tolerance among hallucinogen drugs depends on a similarity of pharmacological effect or on a similarity of chemical structure.

In our experiments (BALESTRIERI and FONTANARI), BOL 148, given at increasing dosages (up to 2 mg. a day) for 4—8 days did not consistently antagonize the effects of LSD 25 (160 mcg.). However, a certain degree of tolerance to LSD 25, at lower dosages than ours (50 mcg. or 1 mcg./kg.), was obtained giving BOL 148 for 5—7 days by ABRAMSON *et al.* (total dosage 0.85—1.45 mg.) and by ISBELL *et al.* (3 mg. a day). A good resistance to LSD 25 (50—75 mcg.) was reported by GINZEL and MAYER GROSS, after only a 1—2 day administration of a few mg. of BOL 148. With a very prolonged administration (4—5 weeks) of BOL 148 at high dosages (30 mg. a day) TURNER *et al.* obtained a complete resistance to LSD 25 (150—200 mcg.). ISBELL *et al.* ruled out competition between LSD 25 and BOL 148, while MURPHREE *et al.* reported that the latter drug antagonized the effect of the former on blood pressure and pupil size, but not on mental conditions. ABRAMSON *et al.* showed that MLD 41, given for 6 days up to 350 mcg., protects man against 100 mcg. of LSD 25. Cross tolerance between LSD 25 and LAE 32 and BOL 148 was reported by CHOLDEN *et al.*, but they did not observe the same phenomenon between LSD 25 and mescaline. HOSKO and TISLOW have not been able to induce a resistance to the blood pressure effects of mescaline in dogs treating them previously with LSD 25. Cross tolerance between LSD 25 and mescaline was observed in rats, by FREEDMAN and AGHAJANIAN.

Former experiments performed by ourselves (BALESTRIERI; BALESTRIERI and FONTANARI) showed that a good degree of cross tolerance seems to exists between LSD 25 and mescaline.

We performed another group of experiments, testing tolerance to LSD 25 after a treatment with UML 491, and tolerance to JB 336 after a treatment with LSD 25. The trials, according to the method previously described (BALESTRIERI and FONTANARI), were carried out on 13 patients, not aware of the experimental design. The diagnosis was polyneuritis, psychoneurosis, multiple sclerosis, myopathia. Controls were possible in 9 of the same subjects and were made before the tolerance trials, or at least 6 days later. Drugs were given orally. In 5 patients, after a treatment with UML 491 for 5—6 days (2—4 mg. a day), the response to LSD 25 (200 mcg.) was very mild. The control with the same dose of LSD 25 was possible in three of the subjects, and it showed a much stronger reaction both from the psychic and the autonomic point of view. In 4 other subjects, a single UML 491 administration (3 mg.) one hour before LSD 25 (150 mcg.) seemed not to antagonize in any way the latter drug. Actually, we have been able to induce only one subject to repeat the trial with LSD 25 alone, at the same dosage, and the reaction was somewhat milder. A simple antagonism between the two drugs seems probably to have been ruled out. In 4 other patients who had acquired a good tolerance to LSD 25 after a prolonged administration of the drug (up to 200 mcg. daily, for 4—8 days) the effect of JB 336 (10 mg.) did not appear consistently different from that obtained in the control performed on each subject with the same dosage of the second drug. The difference was of the same order as in our trials with LSD 25 after a prolonged treatment with BOL 148 (the average decrease was 22% and 12%, respectively).

A few additional experiments were recently performed with LSD 25 and psilocybin. In two psychoneurotic patients, a tolerance to the latter drug (6 mg. intramuscularly) seemed not to appear after a treatment with the former (up to 200 mcg. orally, during 5—8 days). Both cases were controlled with the same dosage of psilocybin. A tolerance to psilocybin seems very difficult to be achieved even with repeated administration of the drug itself. This type of experiment was also performed in other three psychoneurotic patients, with a daily dosage of 3—6 mg. (orally or intramuscularly) for 7—9 days.

On the basis of our present knowledge, cross tolerance among lysergic acid derivatives seems to occur also if the psychotomimetic activity (as with BOL 148 and UML 491) is low or almost absent at the given dosages. Our studies on mescaline suggest that cross tolerance can also depend on similarity of pharmacological effect. However, cross tolerance did not appear, at least with a comparable intensity, in our trials with LSD 25 and JB 336 or psilocybin.

Further controls are needed in order to clarify the problem.

d-Lysergic Acid Diethylamide (LSD 25), 1-Methyl-d-Lysergic Acid Butanolamide (UML 491) and O-Phosphoril-4-Hydroxy-N-Dimethyl Tryptamine (Psilocybin) were kindly supplied by Sandoz Ltd., N-Methyl-3-Piperidyl Benzilate (JB 336) by Leo G. Abood Ph. D.

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