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SINTAMIL ® - A NEW DIBENZOXAZEPINE ANTIDEPRESSANT*

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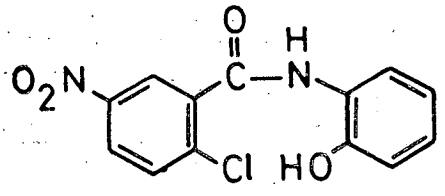
Summary: The synthesis, pharmacology, metabolism and toxicology of the new antidepressant, Sintamil ® - 10-[3-(dimethylamino) propyl]-2-nitro-dibenz[b,f][1,4] oxazepin-11 (10H) one hydrochloride are described.

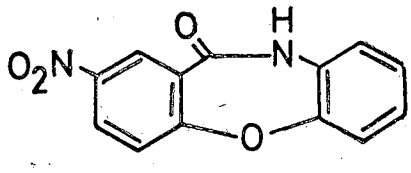
Key words: Sintamil dibenzoxazepine antidepressants

Sintamil (1), a new dibenzoxazepine of structure III, is a psychotherapeutic agent with significant antidepressant and antianxiety activity (2). This communication briefly describes its synthesis, pharmacology, metabolism and toxicology.

Sintamil (III; CIBA 2330-Go) (1) was advantageously synthesized from nitrolactam (II) obtained readily by the base-promoted cyclization of amide (I), according to a new procedure developed in our laboratories (3,4). Addition of 3-dimethylaminopropyl chloride hydrochloride to a solution of II in aqueous alkali-acetone led to the formation of the N-aminoalkyl derivative which was transformed to the crystalline hydrochloride salt (III), m.p. 229-230°.



I



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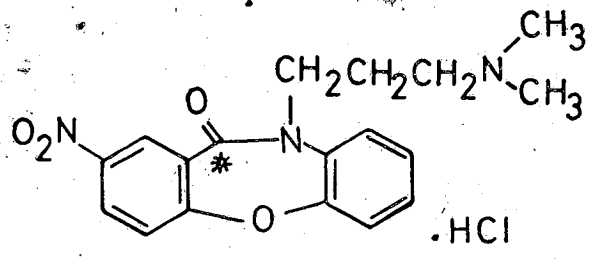
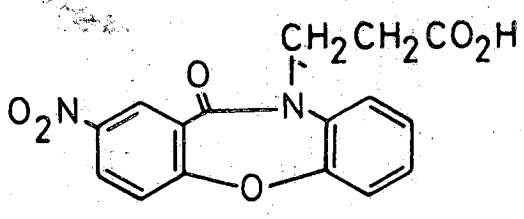


III



IV

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In laboratory tests employed to characterise antidepressant activity, Sintamil and imipramine were quantitatively comparable in antagonising reserpine-induced hypothermia (ED_{50} doses of 1.64 ± 0.55 and 1.28 ± 0.41 *mg/kg* p.o.) and in antagonising tetrabenazine-induced sedation in mice (ED_{50} 23.6 ± 12.46 and 22.49 ± 9.11 *mg/kg* i.p.). Sintamil at 5 *mg/kg* i.p. was twice as effective as imipramine in potentiating the effects of amphetamine on shock-avoidance behaviour in rats. The response to l-dopa in mice was potentiated equally by the two drugs although the dose of imipramine (20 *mg/kg* p.o.) required was twice as large (5).

Sintamil could be qualitatively differentiated from imipramine by virtue of its tranquillizing and sedative effects in various animal species. At an ED_{50} of 2.21 ± 0.55 *mg/kg* p.o., it was thirty times more effective than imipramine (ED_{50} dose 63.8 ± 9.6 *mg/kg* p.o.) in antagonising mescaline induced psychomotor phenomena in mice and its antimescaline activity approximated that of chlorpromazine. It produced a significant and dose-dependent potentiation of hexobarbital-induced sleeping time in mice in the dose range of 1 to 50 *mg/kg* p.o., whereas imipramine did not increase the sleeping time upto 150 *mg/kg* p.o. The conditioned avoidance response (CAR) in trained rats was inhibited by Sintamil at 83 *mg/kg* p.o. whereas CAR was not affected by imipramine upto 100 *mg/kg* p.o. The ED_{50} dose for antiaggressive effects of Sintamil was 80 *mg/kg* p.o. as determined in vicious, septal-lesioned rats as well as in mice exhibiting fighting behaviour elicited by foot shock, whereas equivalent doses of imipramine were ineffective. It was four times as effective as imipramine in reducing spontaneous motor activity in mice, measured by the photo-cell counter technique (5).

Electrophysiological studies in flaxedil-immobilized, procainized and artificially respired cats showed that EEG activation elicited by stimulation of the pontine reticular formation was significantly reduced by 5 to 10 *mg/kg* i.v. of Sintamil, whereas EEG activation induced by mesencephalic or hypothalamic stimulation was unchanged. Electrical after-discharge patterns from septal and amygdaloid areas were also reduced at a dose of 20 *mg/kg* i.v. Potentials evoked from the hippocampus by septal stimulation were facilitated after 1-3 *mg/kg* i.v. but were inhibited at 10 *mg/kg* i.v. Septoamygdaloid evoked potentials were unaltered by lower doses but were significantly inhibited at 20 *mg/kg* i.v. In unanaesthetised cats with permanently implanted subcortical electrodes, a dose of 20 *mg/kg* i. p. had an inhibitory effect on septal and amygdaloid-induced behavioural phenomena as well as on concurrent EEG after-discharge patterns. Quantitative EEG analysis in primate chair habituated monkeys (6) showed that at 25 *mg/kg* p.o., it significantly increased the amount of slow wave sleep and REM and significantly reduced wakefulness. Imipramine at equivalent doses did not influence behavioural or EEG patterns of sleep in the monkey (7). Sintamil was four times less liable to produce convulsions than imipramine. It was also 5 to 10 times less anticholinergic as seen in experiments on pilocarpine-induced salivation in cats (5).

Sintamil (15-50 *mg/kg* i.p.) did not produce any significant change in the catecholamine content of both brain and heart in rats (8). It however, blocked the uptake of ^{3}H-noradrenaline in the rat heart and its ED_{50} as inhibitor of uptake was 4 *mg/kg* i.p. Repeated administration of

Sintamil (2 x 20 *mg/kg* p.o. for 1 to 3 weeks) decreased the turnover rate of noradrenaline as determined after inhibiting its synthesis with α-methyl-tyrosine-methylester (H44/68). The turnover rate of 5-hydroxy-tryptamine was also decreased after single (25 *mg/kg* p.o.) or repeated administration of (2 x 20 *mg/kg* p.o.) Sintamil for 1 to 3 weeks using tyrosine and tryptophan hydroxylase inhibitor (α-propyldopacetamide; H22/54). However, the endogenous 5-hydroxytryptamine content was slightly decreased (25%) after chronic treatment. Guanethidine-induced noradrenaline depletion of the rat heart was antagonised by Sintamil in a dose-dependent manner. No monoamine oxidase inhibitory activity in the brain and liver of the rat was seen upto a dose of 50 *mg/kg* i. p. Owing to its inhibitory effects on the noradrenaline uptake, Sintamil (4 *mg/kg* i. v.) potentiated the pressor responses to adrenaline and noradrenaline in pentobarbitone anaesthetised cats and dogs and also potentiated the nictitating membrane response to adrenaline, noradrenaline and 5-hydroxytryptamine in the cat. The contraction of the guinea pig vas deferens induced by adrenaline and noradrenaline were also increased by pretreatment with Sintamil. It potentiated noradrenaline induced hyperthermia in mice at a dose of 15 *mg/kg* i. p. but per se had no influence on body temperature.

Sintamil did not produce any pronounced effects on the cardiovascular system. In the open-chest dog, it had no effect on cardiac output, stroke volume and total peripheral resistance when infused at a dose of 0.5 *mg/kg* i.v. over a period of 20 minutes.

The metabolic fate of Sintamil was studied in the rat, mouse and monkey (9) using Sintamil carrying a ^{14}C-label as shown by the asterisk in structure III. Both in the rat and monkey, after a single oral dose, the absorption was rapid and excretion occurred to the extent of 75-78% in three days, with the faecal route predominating. Radio autographs of the i.v. treated mouse showed a marked uptake of the label in the brain within a minute of dosing. Reversed isotope dilution analysis of urine and faecal extracts indicated that the pathway of biotransformation of the drug in the rat involved side chain demethylation, loss of side chain with or without concurrent reduction of the nitro to the amino group.

In separate studies in human volunteers (10), the major degradative pathway of Sintamil was seen to be the oxidative deamination of the side chain of the molecule to give an acidic metabolite (IV). The metabolic behaviour of Sintamil thus differs from that of imipramine which in man gives rise to phenolic metabolites and their conjugates(11).

Acute toxicity studies (12) were conducted in six species of animals, viz. rats, rabbits, cats, mice, dogs and monkeys. The oral LD_{50} in rats and mice was 1690 *mg/kg* and 630 *mg/kg* respectively. Dogs tolerated an oral dose of 1200 *mg/kg*. Restlessness, tremors, ataxia and clonic convulsions were the dose-dependent toxic symptoms noticed in all species. In chronic studies rats tolerated doses of 30, 80 and 200 *mg/kg/day* for 6 months. Except reduction in weight gain in the group of male rats treated with high dose, no other toxic effects were noticed. Drug-induced toxic changes were not observed in dogs treated with daily doses of 20, 40 and 80 *mg/kg*

for 6 months. Daily oral administration of the active ingredient of Sintamil to rats af doses of 20, 40 and 60 *mg/kg* did not affect the fertility and reproductive performance of rats. No teratogenic effects were noticed in rats treated with daily doses of 15, 30 and 60 *mg/kg* from day 6-15 of gestation.

Clinical trials in patients have demonstrated that Sintamil is a safe, well tolerated and effective antidepressant.

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