A COMPARATIVE REVIEW OF THE PHARMACOLOGY OF NOMIFENSINE

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- 1 Nomifensine is a new substance which showed, in tests for antidepressant activity, a pronounced effect which is quantitatively better than that of the reference substances.
- 2 With regard to thymoleptic effects in animal studies the effect of nomifensine is similar to that of tricyclic antidepressants, but nomifensine has no pronounced anticholinergic activity.
- 3 Nomifensine influences the cardiovascular system very slightly.
- 4 The mechanism of action of nomifensine differs from that of tricyclic antidepressants and must be clearly differentiated from phenylalkyl amines with sympathomimetic activity.
- 5 Nomifensine is a compound with a special, new profile of action, and thus cannot be classified in known categories.

Special pharmacology

Nomifensine has proved to be a CNS-effective substance in pharmacological screening. The acute toxicity is slight in relation to pharmacologically effective doses (Table 1). Studies on behaviour and motility revealed that low doses of nomifensine reduce motility and have a slightly tranquillizing effect, whereas higher doses increase motility and may cause stereotypic movements. The animals did not become aggressive (Table 2). The dosage range in which— independent of route of administration—depressant effects were observed in various species was 0.1–3.0 mg/kg.

Nomifensine is rapidly absorbed by all routes of administration, and its activity is dose dependent. Nomifensine, given intraperitoneally, antagonized electroshock-induced effects in mice with an ED_{50} of 19 mg/kg. The compound had no effect on nicotine-, metrazole- and strychnine-induced convulsions, and it did not influence alcohol- and hexobarbital-induced sleeping time, whereas tricyclic antidepressants prolonged the sleeping time.

In tests for the demonstration of thymoleptic activity, nomifensine exhibited a good efficacy in comparison with reference substances and in relation to its good tolerability. Its good efficacy after oral treatment must be emphasized. Nomifensine had an antagonizing effect on reserpine-induced hypothermia in mice; it was more effective than imipramine; and its dose-dependence was more clearly demonstrable than that of the reference substance (Figure 1).

Nomifensine also proved to be more effective than imipramine in influencing tetrabenazine- and

reserpine-induced catalepsy in mice and rats. In this respect, it was remarkable that some of the doses effective in these studies were still within the dosage range which did not increase motility in experimental animals (Table 3).

In cats, a subcutaneous dose of reserpine 0.1 mg/kg body weight induces a syndrome characterized by a change in behaviour, the symptoms ranging from increasing inhibition of spontaneous motor activity to the development of catalepsy. Simultaneously, an autonomic syndrome develops in which the animals show miosis, ptosis, prolapse of the nictitating membrane, and hypersecretion of tears and saliva. In studies aimed at eliminating this severe and persistent syndrome, the effects of the same doses of nomifensine and imipramine were compared with each other, and were evaluated using a point system. Subcutaneous doses of nomifensine 5 and 10 mg/kg body weight proved to be more than twice as effective as imipramine (Figure 2).

In an examination of the influence on catalepsy-inducing agents, the criteria were the effects on reflex and autonomic processes. We tried to inhibit the working activity of trained rats with tetrabenazine and to antagonize the resulting inactivity with nomifensine. We assumed that the working activity is a 'conscious' activity. The test in rats was using the operant behaviour model, in which the time needed for pressing the lever a certain number of times was recorded. An intraperitoneal dose of tetrabenazine 3 mg/kg body weight suppressed the working activity almost completely, although there seemed to be no change in spontaneous behaviour. A subcutaneous

Figure 1 Influence of nomifensine on reserpine-induced hypothermia in mice ($n = 10$ per dose). ●, Nomifensine 10 mg/kg s.c.; ▲, 5 mg/kg s.c.; □, 2.5 mg/kg s.c.; ○, imipramine 10 mg/kg s.c.; △, 5 mg/kg s.c.; ■, 2.5 mg/kg s.c. Analysis of variance; nomifensine compared with control; imipramine compared with control; nomifensine compared with imipramine $P < 0.05$.

Table 1 Acute toxicity (24-h values)

Nomifensine	DL ₅₀ (mg/kg)
Mouse i.v.	90 (83- 98)
orally	400 (315-508)
Imipramine	
Mouse i.v.	54 (51- 57)
orally	450 (390-518)

Table 2 Effect of nomifensine on motility

<i>Decrease of spontaneous motility</i>	<i>Dosage range (mg/kg)</i>
Mouse	0.1-3.0 i.p.
Rat	0.5-2.5 orally
Monkey	0.1-0.3 s.c.
<i>Slight tranquillizing activity</i>	
Hamster	0.125-0.5 orally

Table 3 Antagonistic effect against catalepsy

<i>Test</i>	<i>ED₅₀ (mg/kg orally) (30-90 min after administration)</i>
Reserpine-induced catalepsy in rats	6.8 (5-10) Nomifensine 18.6 (15-25) Imipramine
Tetrabenazine-induced catalepsy in mice	5.6 (4- 9) Nomifensine 20.5 (16-24) Imipramine

$n = 10$ per dosage and control group.

Figure 2 Intensity of reserpine-induced syndrome after treatment with nomifensine and imipramine in cats. Evaluation using a point system. Dotted columns, Imipramine 10 mg/kg s.c.; hatched, 5 mg/kg s.c.; solid nomifensine 10 mg/kg s.c.; cross-hatched, 5 mg/kg s.c.; open, reserpine 0.1 mg/kg s.c. controls ($n = 8$).

dose of nomifensine 5 mg/kg body weight, given 1 h after administration of tetrabenazine, restored the working activity of the rats, and the animals worked only slightly slower than untreated controls. In this test, the same dose of imipramine was ineffective.

The influence on the reserpine-induced syndrome in cats and the restoration of the tetrabenazine-blocked working activity in rats by a single treatment with nomifensine proves the rapid onset of action of this compound.

In addition, examinations were carried out to determine whether repeated administration of nomifensine changes its antagonistic activity against reserpine. The evaluation criterion was the influence of nomifensine on reserpine-induced hypothermia and reserpine-induced ptosis in mice. The effect on animals which had received nomifensine 16 mg/kg i.p. once daily for 5 d was compared with the effect in a control group which had received placebo treatment for 4 d and had then received a dose of nomifensine on day 5. No significant difference between the effects after repeated or single treatment was observed.

In contrast to tricyclic antidepressants, nomifensine does not have a pronounced anticholinergic activity. It has an antagonistic influence on oxotremorine-induced hypothermia (ED_{50} 10.5 mg/kg orally, 1–3 h), but it does not inhibit oxotremorine-induced tremor. The effect of nomifensine on carbachol-induced contractions of guinea-pig isolated ileum is very slight. Effective doses were higher than 10^{-5} M. The influence of nomifensine on the effect of catecholamines was examined using several test models.

In a dosage range of 0.25–2.0 mg/kg i.v., nomifensine potentiated the pressor response to noradrenaline (NA) in cats, but it had no influence on blood pressure. Nomifensine was more effective than

imipramine. Three- to fivefold dosages of imipramine were necessary to achieve the same effect as nomifensine; besides, imipramine caused a decrease in blood pressure (Figures 3 and 4).

The potentiating effect of nomifensine on the response of the nictitating membrane of cats to adrenaline and NA was slightly stronger than the effect of desmethyl-imipramine (DMI). The effect of nomifensine was already clearly demonstrable after intravenous administration of 0.1 mg/kg, whereas the same dose of DMI was not sufficient to produce a significant effect.

Nomifensine 10^{-6} M potentiated NA-induced contraction in cat isolated spleen strip. Compared with DMI, nomifensine—given in the same concentration—proved to be 30% more effective. Nomifensine did not have an intrinsic contraction-inducing effect on the spleen.

Pretreatment of dogs with nomifensine or DMI had a quantitatively comparable inhibitory effect on tyramine-induced increase in blood pressure and heart rate. The same pretreatment blocked the response of cat nictitating membrane to tyramine.

We obtained preliminary information regarding the mechanism of action of nomifensine in studies in which the influence on catecholamine metabolism was tested.

Similar effects of both substances observed in several test models permit the conclusion that they have a similar site of action. Their common effect on tyramine indicates an identical mechanism for action in nomifensine and DMI. The results obtained in whole-animal studies have already revealed that nomifensine, like DMI, is an uptake inhibitor because the effect of tyramine, which eliminates NA from synaptosomes, may be attenuated or suppressed

Figure 3 Influence of nomifensine on pressor reaction to NA in cat. Arrows, NA 0.6 µg/kg i.v.; double arrow, nomifensine 0.5 mg/kg i.v.

Figure 4 Influence of imipramine on pressor reaction to NA in cat. Arrows, NA 0.6 μ g/kg i.v.; double arrow, imipramine 2.5 mg/kg i.v.

Figure 5 Influence of nomifensine on tyramine-induced pressor reaction in dog. Arrow, Nomifensine 2.5 mg/kg i.v.; Tyr, tyramine 0.2 mg/kg i.v.

Figure 6 Influence of nomifensine injected intraperitoneally on motor activity in rat. Pretreatment: hatched columns, saline; dotted, α -methyl-*p*-tyrosine (100 mg/kg).

completely by pretreatment with uptake inhibitors. After pretreatment with a monoamine oxidase (MAO) inhibitor, the effect of tyramine on blood pressure would be unchanged or increased.

Further studies were carried out to clarify the mechanism of CNS stimulation by nomifensine, observed in animals after administration of higher doses. Increase in rat motility was chosen as the criterion for this effect, and amphetamine and apomorphine served as reference substances. Motility increase in rats which had received nomifensine, amphetamine, or apomorphine was compared with that in animals which had been pretreated with α -methyl-*p*-tyrosine (α -MPT), reserpine or a combination of both substances. The results show that—in contrast to amphetamine—the stimulating effect of nomifensine was not affected by blocking the

Figure 7 Influence of nomifensine injected intraperitoneally on motor activity in rat. Pretreatment: hatched columns, saline; dotted, reserpine 5 mg/kg; cross-hatched, α -MPT; open, reserpine and α -MPT 25 mg/kg.

Figure 8 Guinea-pig ECG. Intravenous infusion. Prolongation of PQ time. ○, Nomifensine 1 mg/kg/min i.v.; ●, nomifensine 3 mg/kg/min i.v.; ■, imipramine 1 mg/kg/min i.v.; ▲, amitriptyline 1 mg/kg/min i.v.

catecholamine synthesis with α MPT (Figures 6 and 7); neither was the apomorphine-induced hypermotility influenced. Pretreatment with reserpine caused an increase in motility. A combination of α -MPT and reserpine blocked the nomifensine- and amphetamine-induced stimulation.

Nomifensine proved to be a DA agonist in further pharmacological studies. I will not go into further detailed discussion of the results here, as these topics are covered by other papers in these proceedings.

EEG recordings in cats and rabbits showed an increase in vigilance.

General pharmacology

The effect of nomifensine on the cardiovascular system was examined particularly carefully, as tricyclic antidepressants are known to cause, among other side-effects, disorders in the cardiovascular system.

Table 4 Cardiovascular subchronic study in dogs treated with nomifensine 3 mg/kg/d orally for 14 days

Parameters examined before and after treatment:

Blood pressure
Pressure in left ventricle
 dP/dt
ECG
Heart rate
Cardiac output

Result: no significant differences between values before and after treatment with nomifensine

Table 6 Other effects of nomifensine

Nomifensine has no effect on:

Gastro-intestinal motility	Temperature
Choleresis	Blood glucose
Diuresis	Intra-ocular pressure

Nomifensine does not have a lipolytic effect

Nomifensine has a very slight effect on:

Sensitivity to pain (analgesic)
Inflammatory processes (anti-inflammatory)

Table 5 Influence on contractile force of guinea-pig isolated heart

Dose	Nomifensine	Amitriptyline	P
10	- 6.8% (n = 13)	-29.3% (n = 12)	<0.001
50	-16.9% (n = 7)	-61.0% (n = 5)	<0.001
100	-33.0% (n = 10)	-69.8% (n = 4)	<0.001
<i>Imipramine</i>			
10	- 6.8% (n = 13)	-29.6% (n = 12)	<0.001
50	-16.9% (n = 7)	-54.9% (n = 8)	<0.01
100	-33.0% (n = 10)	-77.8% (n = 5)	<0.001

Dose = μ g mixed with perfusion liquid.

% = decrease in contractile force in relation to initial value.

Figure 9 Guinea-pig ECG. Intravenous infusion. Prolongation of QRS time. ○, Nomifensine 1 mg/kg/min i.v.; ●, nomifensine 3 mg/kg/min i.v.; ■, imipramine 1 mg/kg/min i.v.; ▲, amitriptyline 1 mg/kg/min i.v.

In an acute study in dogs, nomifensine was administered intravenously in doses of 1–10 mg/kg. The recordings of arterial blood pressure, heart rate and blood flow through the arteria femoralis and the arteria carotis communis showed that doses of nomifensine up to 2 mg/kg body weight had no effect on the cardiovascular system, whereas nomifensine 3–10 mg/kg body weight had only a very slight, transient effect. Dosages of 2–5 mg/kg of the reference compound imipramine had a marked hypotensive and cardiotonic effect, and the blood flow through head and legs was slightly reduced for a short period.

In a study in which dogs received nomifensine 3 mg/kg/d orally for 14 d, the following parameters

were measured both at the start and at the end of the study (Table 4): blood pressure; pressure in the left ventricle; dP/dt ; heart rate; cardiac output. No significant differences were observed between values measured before and after treatment with nomifensine.

In guinea-pig isolated heart, nomifensine influenced the contractile force far less than amitriptyline or imipramine (Table 5).

Nomifensine, amitriptyline and imipramine were administered to guinea-pigs by slow intravenous infusion. The two tricyclic compounds had a pronounced effect, that is, they prolonged the PQ and QRS intervals in the ECG, whereas nomifensine had a

Figure 10 Influence of nomifensine and amphetamine on stomach emptying in rat 30 min after oral treatment. Hatched column, Amphetamine 5 mg/kg; cross-hatched, 10 mg/kg; dotted, nomifensine 5 mg/kg; solid, 10 mg/kg; open, control.

slight effect on these parameters only after the dose was tripled (Figures 8 and 9).

In dogs and rats the influence of nomifensine on stomach emptying was examined. Amphetamine, which is known to cause a marked retardation in stomach-emptying time, served as reference substance. Both compounds were given in an intravenous dose of 0.5 mg/kg to dogs and in oral doses of 5 and 10 mg/kg to rats. In contrast to amphetamine, nomifensine did not influence the

gastric motility (Figure 10).

Further examination of the influence on bodily function and organ systems revealed that nomifensine did not have any influence on: intestine passage; bile secretion; diuresis; saluresis; intra-ocular pressure; body temperature; blood glucose.

Nomifensine has no lipolytic activity, and it has only a slight analgesic and anti-inflammatory effect (Table 6).

Further Reading

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