Pharmacokinetic, behavioural, hyperthermic profile and LD50 of MDAI

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Cathinones and other designer drugs

New psychoactive substances in Europe. An update from the EU Early Warning System (March 2015), 2015.

Smith et al. 2015. An overview of recent developments in the analytical detection of new psychoactive substances (NPSs). Analyst, 140, 4932.
Nonneurotoxic Tetralin and Indan Analogues of 3,4-(Methylenedioxy)amphetamine (MDA)

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Four cyclic analogues of the psychoactive phenethylamine derivative 3,4-(methylenedioxy)amphetamine were studied. These congeners, 5,6- and 4,5-(methylenedioxy)-2-aminoindan (3a and 4a, respectively), and 6,7- and 5,6-(methylenedioxy)-2-aminotetralin (3b and 4b, respectively) were tested for stimulus generalization in the two-lever drug-discrimination paradigm. Two groups of rats were trained to discriminate either LSD tartrate (0.08 mg/kg) from saline, or (+)-MDMA-HCl (1.75 mg/kg) from saline. In addition, a 2-aminoindan (5a) and 2-aminotetralin (5b) congener of the hallucinogenic amphetamine 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) were also evaluated. None of the methylenedioxy compounds substituted in LSD-trained rats, while both 3a and 3b fully substituted in MDMA-trained rats. Compounds 4a and 4b did not substitute in MDMA-trained rats. Compounds 5a and 5b did not substitute in MDMA-trained rats, although 5a substituted in LSD-trained rats, but with relatively low potency compared to its open-chain counterpart. In view of the now well-established serotonin neurotoxicity of 3,4-(methylenedioxy)amphetamine and its N-methyl homologue 1, 3a and 3b were evaluated and compared to 1 for similar toxic effects following a single acute dose of 40 mg/kg sc. Sacrifice at 1 week showed that neither 3a nor 3b depressed rat cortical or hippocampal 5-HT or 5-HIAA levels nor were the number of binding sites \( B_{max} \) depressed for \(^{3}H\)paroxetine. By contrast, and in agreement with other reports, 1 significantly depressed all three indices of neurotoxicity. These results indicate that 3a and 3b have acute behavioral pharmacology similar to 1 but that they lack similar serotonin neurotoxicity.

We have recently described the effects of 1-(1,3-benzodioxol-5-yl)-(methylamino)butanamine (2; MBDB) and compared them with those of the hallucinogens LSD and MDA and with those of the novel psychoactive agent 3,4-(methylenedioxy)methamphetamine (1; MDMA). The essential findings to establish a new pharmacological category.

Although MDMA was advocated as a useful adjunct to psychotherapy, its nonpatentability, recreational popularity, and production of serotonin neurotoxicity in rodents and primates make it unlikely that MDMA will be employed clinically. Therefore, we have begun to search for substances that may have similar therapeutic potential, but which will lack neurotoxicity in animal models.

We were encouraged in this endeavor by the findings.

A synthetic chemical known as MDAI has already emerged as a successor to the drug mephedrone, which was banned in Britain this weekend.
Aminoindans

2-AI  MDAI  MMAI  5-IAI

<table>
<thead>
<tr>
<th>Drug</th>
<th>$ED_{50}$</th>
<th>Neurotoxic?</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>MDMA (μmol/kg)</td>
<td>MBDB (μmol/kg)</td>
<td></td>
</tr>
<tr>
<td>MDA</td>
<td>4.06</td>
<td>2.07</td>
<td>yes</td>
</tr>
<tr>
<td>MDMA</td>
<td>3.41</td>
<td>3.38</td>
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<tr>
<td>MBDB</td>
<td>4.16</td>
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<td>MDAI</td>
<td>2.66</td>
<td>2.04</td>
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<td>2.74</td>
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<tr>
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<td>3.77</td>
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<tr>
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<tr>
<td>6-CAT</td>
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<tr>
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<td>3.91</td>
<td>1.82</td>
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<tr>
<td>5-IAI</td>
<td>2.19</td>
<td>2.67</td>
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</table>

Experimental protocol

- MDAI purchased via internet
- Confirmation of the structure (initial purity cca 90%), converted to hydrochlorid & purified (99.18 %) at Alfarma s.r.o.
- Doses were chosen according to the
  - internet search (published studies and user reports)
  - comparable to those used by humans as well as several times higher (acute toxicity)
  - previous experiments in our lab with 2C-B, PMMA, MDMA
- Behavioural study - MDAI 5, 10, 20 & 40 mg/kg s.c.
  - 2 time intervals from drug administration - 15 and 60 min
- Pharmacokinetics – 10 mg/kg s.c.
- Metabolism 20 mg/kg s.c. / 24h urine
- LD 50 – s.c., i.v. and gastric probe
Pharmacokinetics

Single bolus dose 10 mg/kg s.c.
Metabolism

Main metabolic pathway: cytochrome P450 catalysed O-demethylenation to DHAi and subsequent methylation by catechol-O-methyltransferase to HMAi.

Metabolic pathways of MDAI

I. oxidative demethylenation
II. N-acetylation
III. Catechol monomethylation
IV. Hydroxylation
V. Deamination
VI. Sulphation
VII. β-glucuronidation.

Open field experiments

Locomotor activity
EthoVision (Noldus)
arena (68 cm x 68 cm x 30 cm)
Registration for 30 min.
Open field experiments

90% Animals treated with 40 mg/kg died cca 60-90 min after treatment.
Open field experiments

**Prepulse inhibition of acoustic startle (PPI)**

- **Wistar rats** b.w. 200 – 250 g
- **Apparatus:** SR-Lab, San Diego instruments, California (SDI)
- Background noise 70 dB
- Pulse 116 dB
- Prepulse 78 and 86 dB
- prepulse-puls interval 30, 60 and 120 ms
- 5 min acclimatization period
- Duration cca 20 min

- the ability of a preceding weak sensory event to inhibit reaction to another consequent intense stimulus
- magnitude of motor response

**Time**

- 5 min acclimatization 70 dB
- Session 2 & 3 78dB pp
- Session 1 & 4 – 7 116dB puls alone
- 86dB pp
Prepulse inhibition of acoustic startle (PPI)

Effects on thermoregulation

- Ecstasy like drugs typically increase body temperature – **serotonergic effect**
- Temperature increases more in clubs while dancing - increased risk of hyperthermia and toxicity
- Same effect found for animals with MDMA and other drugs
- Measured for 10 hours
- 1 h intervals of measurement mostly
- During the first 2 hours after drug administration 0.5h intervals
- Rectal temperature
- Animals housed isolated and in groups of 5
- Comparable design to our previously published for PMMA

Palenicek te al. Pharmacology, Biochemistry and Behavior. 98 (2011) 130–139
Thermoregulation

Methylone 10 & 20 mg/kg

MDAI 10 & 20 mg/kg

(A) Methyleone 10 mg/kg
(B) Methyleone 20 mg/kg

Vehicle

temperature in °C

time of administration

VEH

10mg/kg MDAI

20mg/kg MDAI

07.00 08.00 09.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 am am pm pm pm pm

13.00 14.00 15.00 16.00 17.00 pm pm pm pm pm pm pm

in groups by 5 in a cage
Perspiration

Creatinine (A) blotter paper 90 min after treatment, (B) blank urine, (C) fur before treatment, (D) fur after treatment, (E) saliva
Toxicity, LD50

Autopsy after 40 mg/kg s.c. in dead animals:
- Signs of DIC
- Brain oedema
- Microthrombi in organs

After 20 mg/kg s.c. (additional animals):
- Signs of hyperaemia in organs.
- Signs of shock necrosis in liver
- Smears around mouth and nose contained erythrocytes

Behavioural observations:
- Flat body posture, sweating, hyperactivity
- Bleeding from nose and mouth
- Seizures
- Anaemic limbs

Histological images:
- A: Heart tissue
- B: Normal heart tissue
- C: Kidney tissue with signs of injury
- D: Kidney tissue with normal appearance
Emerging toxicity of 5,6-methylenedioxy-2-aminoindane (MDAI): Pharmacokinetics, behaviour, thermoregulation and LD50 in rats

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ABSTRACT

MDAI (5,6-Methylenedioxy-2-aminoindane) has a reputation as a non-neurotoxic ecstasy replacement amongst recreational users, however the drug has been implicated in some severe and lethal intoxications. Due to this, and the fact that the drug is almost unexplored scientifically we investigated a broad range of effects of acute MDAI administration: pharmacokinetics (in sera, brain, liver and lung); behaviour (open field; prepulse inhibition, PPI); acute effects on thermoregulation (in group-/individually-housed rats); and systemic toxicity (median lethal dose, LD50) in Wistar rats. Pharmacokinetics of MDAI was rapid, maximum median concentration in serum and brain was attained 30 min and almost returned to zero 6 h after subcutaneous (sc) administration of 10 mg/kg MDAI; brain/serum ratio was 4. MDAI rapidly accumulated in hepatocytes in the open field. MDAI (5,48,30 and 48 mg/kg) increased...
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Thank you for attention