NEUROPHARMACOLOGICAL COMPARISON BETWEEN DOMPERIDONE AND METOCLOPRAMIDE

A. WAUQUIER, C.J.E. NIEMEGEERS and P.A.J. JANSSEN
Department of Pharmacology, Janssen Pharmaceutica, B-2340 Beerse, Belgium

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Abstract—Domperidone, a new gastrokinetic with potent antiemetic properties is devoid of central effects, up to high dose levels. To assess the CNS activity of domperidone and metoclopramide, the inhibition of intracranial self-stimulation (ICS) in two different situations, and the influence on EEG in dogs were studied. The dissociation between the antiemetic and central effects of both compounds were evaluated in dogs given a stereotypogenic dose of apomorphine. A significant and dose-related inhibition of ICS (conditioned situation) was obtained with 0.8 and 1.6 mg/kg i.v. domperidone and with 0.125, 0.25 and 0.50 mg/kg i.v. metoclopramide. The ED50 values were 0.79 mg/kg and 0.25 mg/kg respectively. The effect was most pronounced 4 hr after administration with domperidone and 15 min after administration with metoclopramide. In the EEG studies, no specific structure-related effects were found but the total potency was increased with domperidone 0.8 and 1.6 mg/kg i.v. and with metoclopramide 0.063, 0.125, 0.25 and 0.50 mg/kg i.v. This increase was due to a decrease in fast frequencies, an increase of slower frequencies and a slight increase of the amplitude. Sleep-like patterns were not observed with either compound. In the apomorphine-test in dogs, the ratio between the i.v. ED50 values for antagonism of stereotypy and of emesis was 180 (1.8/0.01) for domperidone and 2.67 (0.64/0.24) for metoclopramide. Thus, central effects and antiemetic effects are concomitant with metoclopramide, whereas with domperidone, extremely large doses are required to obtain central effects.

Domperidone, 5-chloro-1-{1-[3-(2, 3-dihydro-2-oxo-1H-benzimidazol-1-yl)propyl]-4-piperidinyl}-1,3 dihydro-2H-benzimidazol-2-one, is a new gastrokinetic with potent antiemetic properties. Domperidone is reportedly effective for functional gastrointestinal disorders, such as dyspepsia, gastroesophageal reflux, nausea and vomiting (1–2).

In in vitro experiments on the isolated guinea-pig stomach, domperidone selectively inhibited the relaxation induced by intra-arterial dopamine (3). The latter experiment suggests that dopamine is involved in the local feedback control of gastric motility and that the gastrokinetic effect of domperidone can be explained by its interference with dopamine receptors, at the level of the stomach.

In in vitro binding assays, domperidone was found to be a potent and specific dopamine antagonist, but ex vivo and in vivo
binding experiments showed that domperidone did not reach the dopamine receptors in the rat striatum (4).

Given intracerebrally, domperidone acted as a potent dopamine antagonist (5), but given systemically, extremely large doses were required to observe central effects (1). All these studies suggested that domperidone cannot readily cross the blood brain barrier.

In the present experiments, domperidone and metoclopramide were studied in the dog in a number of tests indicative for central activity: intracranial self-stimulation, electroencephalography and apomorphine-induced stereotypy. The difference between the antiemetic ED50 and the antistereotypic ED50, measured in the same dogs given a high dose of apomorphine was used as a measure of dissociation between peripheral and central activity of both compounds.

MATERIALS AND METHODS

Subjects: The subjects were 15 adult male inbred Labrador dogs (self-stimulation experiments), 7 adult male inbred Beagle dogs (electroencephalography) and 6 adult inbred Beagle dogs of both sexes (stereotypy and emesis).

Surgery: For the intracranial self-stimulation experiments and EEG, dogs were implanted as described previously (6). In short: the dogs were premedicated with 5 ml Hypnorm® s.c., followed by 5 ml Nembutal i.v. (pentobarbital natrium, 60 mg/ml). The animals were positioned in a stereotaxic apparatus (David Kopf Instruments), immediately intubated, connected to a respirator (Bird, Mark 4) and artificially ventilated with the aid of a nitrous oxide oxygen blender (N₂O: 75%, O₂: 25%) (Bird).

For the EEG experiments, dogs were implanted with cortical (surface) and subcortical (depth) electrodes. Surface electrodes were stainless steel screws (one in the bone of the skull in the frontal region, a second in the temporal region and a third in the occipital region). Depth electrodes consisted of a stainless steel needle (0.5 mm diameter, insulated except for 1/2 mm of the tip) and an insulated stainless steel wire (0.2 mm diameter). The wire was inserted into the needle such as to protrude 1/2 mm beneath the tip of the needle. Depth electrodes were implanted in the caudate nucleus, basolateral amygdala, dorsal hippocampus and oral pontine reticular formation. Coordinates of the depth electrodes were determined according to the stereotaxic atlas of Dua-Sharma et al. (7) and corrected for individual skull dimensions.

For the self-stimulation experiments, depth electrodes were placed in the lateral preoptic region, nucleus accumbens, lateral hypothalamus both brain sites and in some dogs an additional electrode was placed either in the substantia nigra, basolateral amygdala or the posterior hypothalamus (8).

After surgery, the dogs were placed in a recovery room and treated daily with Dicatrepton 1500, i.m., for at least 5 days. After two weeks of recovery, the dogs were regularly transferred to the experimental room in order to adapt to the environment. The experiments were begun at the earliest 1 month after surgery.

Intracranial self-stimulation (ICS): After recovery, dogs were trained to press a lever, which triggered electrical brain-stimulation, through a swivel-device which permitted the animal to move freely in a 0.9 x 1.15 m cage, without twisting the electrode leads. The electrical stimulation consisted of a 500-msec train of biphasic square wave pulses at a rate of 300 pulses per second, each pulse had a duration of 1 msec and an intensity of...
less than 0.5 mA. After establishing self-stimulation, the dogs were further trained according to one of the following procedures: a) free situation: the dogs were allowed to press a lever in the cage described above, for n times 10-min periods, n being the number of electrodes tested in a dog; an interval of 3 min without brain-stimulation, separated each period (9): b) conditioning situation: the dogs were partially restrained in a ‘pavlovstand’ and allowed to press a lever for brain-stimulation according to the following procedure: each session consisted of 20 trials of 20 sec during which brain-stimulation was available upon a tone of 1,000 Hz (conditioned stimulus or CS) spaced with an interval of 30 sec, during which lever-pressing had no programmed consequences (6).

After stabilization of lever pressing behaviour, experimental sessions were held on Monday, Wednesday and Friday. At least two sessions separated each drug treatment. In procedure a) dogs were given domperidone, either subcutaneously, orally or intravenously and metoclopramide intravenously (see Table 2). In procedure b) dogs were given i.v. either domperidone or metoclopramide (see Fig. 1). These dogs were injected only once per week (on Wednesdays) according to the following sequence: 1st dose of domperidone, 1st dose of metoclopramide, 2nd dose of domperidone, 2nd dose of metoclopramide, etc. Sessions were run 15 min and 4 hr after drug injections.

Electroencephalography (EEG): The dogs were kept unrestrained in a shielded cage and the electrodes were connected to a mingograph. The EEG was recorded on a 12-channel Elema-Schönander at a paper speed of 15 mm/sec. Filters and time constant was set at respectively, 70 Hz and 0.3 sec. All derivations were bipolar i.e. between the tube and internal wire for the depth electrodes and between frontal-temporal, frontal-occipital and temporal-occipital for the cortical electrodes.

Recordings were taken for 5-min periods: 60 min and 30 min before injection and at 0–5, 5–10, 10–15, 30–45, 45–60 and 60–65 min after injection. Three additional 5-min periods were taken 4 hr after injection of the two highest doses of domperidone and metoclopramide.

Power spectral analysis of 4 channels was done on-line with the aid of a PDP 11/E10 minicomputer system (Digital Equipment Corporation) (10). In short, the EEG-signal (7 channels) is digitized in the analogue to a digital converter and processed by the computer. Digitizing, at a rate of 5 msec, allowed a frequency pass band of 0 to 100 Hz.

A Fast-Fourier program transforms an epoch of 1024 sample points (5.12 sec) to the amplitude-frequency domain. To reduce the results obtained by the Fast-Fourier transformation, the power of each harmonic is computed and accumulated in 7 defined frequency bands (resolution ±0.2 Hz): 0.5–3.5 Hz (delta), 3.5–7.5 Hz (theta), 7.5–9.5 Hz (alpha 1), 9.5–13.5 Hz (alpha 2), 13.5–17.5 Hz (beta 1), 17.5–25 Hz (beta 2), 25–40 Hz (beta 3). The total signal (4.6 min) was divided into 9 periods consisting of 6 subsequent epochs (each epoch lasting 5.12 sec). Six medians of the corresponding epochs of each of the 9 periods were calculated, i.e. the median of the 1st, the median of the 2nd, ..., the median of the last (6th) epoch of each period. This technique was introduced to eliminate extremely high and low values, caused by movement artifacts or by the variety of the signal. Finally, the mean power, standard deviation and standard error of the 6 medians were computed for each of the 7 defined frequency bands. These values are the estimates of the power in the different bands for the 4.6-min period. They were printed on the printer device and recorded on a disk.
The analysis was repeated for each time period, for each of the 4 channels and for each of the 7 dogs.

The absolute powers thus found, are subjected to interindividual variability, originating from different recording sensitivities, electrode impedances, etc. Therefore, statistical analysis was performed on normalized powers. The total power obtained with each dog during the second control period was equalized at 100 mW, which provides a correction factor by which the power obtained in each frequency band and at each time period was multiplied.

Dogs were treated i.v. only once a week with either 0.2, 0.4, 0.8 and 1.6 mg/kg of domperidone or 0.063, 0.125, 0.25 and 0.50 mg/kg of metoclopramide.

Inhibition of stereotypy and antagonism of emesis: Inhibition of stereotypy (11) and antagonism of emesis were assessed over a period of 3 hr after the injection of apomorphine HCl 1.25 mg/kg s.c. Stereotypy was observed every 5 min and the results were expressed in terms of the following scores: pronounced +++, obvious ++, dubious +, and absent 0. Complete protection from emesis and complete absence of stereotypy were the criteria used for the calculation of the ED50 values.

Six Beagle dogs were treated at weekly intervals with increasing i.v. doses of domperidone or metoclopramide; 3 dogs were first given domperidone, and the other 3 dogs metoclopramide. The doses in mg/kg of domperidone and metoclopramide, given in these experiments are shown in Table 3.

**Compounds:** Intravenous administration was given into the vena saphena and the solutions used were prepared from clinically available ampoules of domperidone (2 mg/ml) and metoclopramide (5 mg/ml), as shown in Table 3. The subcutaneously and oral administrations (by gavage) were 0.5 ml/kg. For oral administration, freshly prepared homogeneous aqueous suspensions of domperidone containing 1% polysorbate 80 and 0.5% sodium carboxymethyl cellulose were used.

**RESULTS**

**Intracranial self-stimulation (ICS):** Table 1 shows the electrode partition in the dogs used in the different ICS experiments. There was no significant difference in inhibition between the different electrodes and therefore the effects of all electrodes were combined.

**Free-situation (procedure a).** Table 2 shows the mean percentage of lever-pressing for brain stimulation as compared to the controls. With domperidone, no statistically significant inhibition was obtained. The highest doses tested were 0.63 mg/kg s.c., 20 mg/kg or/and 1.6 mg/kg i.v. With this last dose, the response rate was reduced by

<table>
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<th>Table 1. Partition of electrode localization in the dogs used in the self-stimulation experiments</th>
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<td><strong>Route</strong></td>
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<td>Free situation</td>
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<td>s.c.</td>
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<td>or.</td>
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<td>i.v.</td>
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<td>Conditioning situation</td>
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<td>i.v.</td>
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<td>Total</td>
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With metoclopramide i.v. a dose-related inhibition was found, the ED50 value being 0.20 mg/kg.

## Conditioned situation (procedure b).

Figure 1 shows the mean percentage of lever pressing for brain stimulation, as compared to the controls, assessed 15 min and 4 hr after i.v. domperidone and metoclopramide. A significant and dose-related inhibition of ICS was obtained with 0.8 and 1.6 mg/kg i.v. domperidone 15 min, and was even more pronounced, 4 hr after injection. Inhibition of ICS with i.v. metoclopramide was obtained at 0.125, 0.25 and 0.50 mg/kg 15 min after injection. Four hours after injection, a slight inhibition was still obtained at the highest dose level of 0.5 mg/kg.

The doses inhibiting ICS to 50% of the control values are for domperidone 0.79 mg/kg and for metoclopramide 0.25 mg/kg. The ratio between the inhibition of ICS and the antiemetic activity for domperidone is 272 (0.79/0.029 mg/kg) (lowest i.v. ED50 obtained in the standard apomorphine antagonism test 6), for metoclopramide the ratio is 3.5 (0.25/0.71 mg/kg).

### Electroencephalography:

There were no specific structure-related effects, but an overall increase in potency was evident and was most pronounced in the frontal-temporal cortex. Therefore the normalized power (total power obtained during the control period equalized to 100) obtained in the frontal-temporal cortex only is shown in Fig. 2.

![Fig. 1. Percentage lever-pressing for brain-stimulation as compared to the controls, obtained 15 min and 4 hr after different doses of domperidone and metoclopramide given i.v. to 5 dogs.](image)
Fig. 2. Normalized potency (total potency obtained during the second control period equal to mW) obtained with 7 dogs during control periods and of different time intervals after i.v. administration of 4 doses of domperidone (upper figure) and metoclopramide (lower figure).
Domperidone in doses 0.2 and 0.4 mg/kg i.v. did not significantly affect the EEG. Higher doses 0.8 and 1.6 mg/kg increased the total potency in all channels, but the individual variability was rather high. The increase in total potency was mainly due to an overall decrease of fast frequencies (beta-rhythm), the appearance of lower frequencies and an increase of amplitude (in the theta-, and alpha 1-band). There was no indication of sleep EEG patterns, characterized by high amplitude delta- and theta waves and spindling.

Metoclopramide intravenously increased the total potency, at all dose levels (Fig. 2), but the interindividual variability again was pronounced. The higher total power was mainly due to an increased power in the delta- and theta-frequency band. This increment results from a decrease of fast frequencies and an increase of slower activity, but sleep-patterns were not evident.

Stereotypy and emesis: The results obtained in the stereotypy test are shown in Table 3. The ED50 for domperidone protecting against apomorphine-induced emesis is 0.010 mg/kg. Emesis in this test is induced by 1.25 mg/kg s.c. apomorphine. This dose is 4 times higher than the currently used dose in the standard apomorphine antagonism test (1). Apomorphine-induced stereotypy is blocked by 1.80 mg/kg, a dose 180 times higher. With metoclopramide the ED50 for protection against emesis is 0.24 mg/kg and for blockade of stereotypy: 0.64 mg/kg, that is a dissociation ratio of 2.67.

DISCUSSION

The most potent antiemetics known are neuroleptics (12). These compounds, however, are also potent inhibitors of conditioned behaviour, including intracranial self-stimulation (3) and potent antagonists of induced stereotypy (12). In general, neuroleptics were found to block the emetic activity induced by apomorphine, but were devoid of antiemetic activity against copper sulphate-induced emesis. Apomorphine which induces emesis by stimulation of the chemoreceptor trigger zone, which is situated in the area postrema of the 4th ventricle was called therefore a central emetic, in contrast to copper sulphate, which was called a peripheral emetic inducing reflex vomiting.

Since the discovery of domperidone, which is the prototype of a new chemical class of compounds with antiemetic properties in the apomorphine test at very low doses, but with central effects only at much higher doses (1, 2), in the dog, the chemoreceptor trigger zone is situated outside of the blood brain barrier and therefore the antiemetic effect against apomorphine can no longer be termed centrally mediated. Metoclopramide is a neuroleptic, and in spite of its pronounced central effects is used clinically as an antiemetic (13).

With regard to intracranial self-stimulation, domperidone given 1 hr before the session by different routes of administration, was virtually inactive. Metoclopramide, however, did inhibit ICS within one hour after injection at a dose comparable to the given dose of the antiemetic.

Given i.v. 4 hr before testing, domperidone dose-relatedly inhibited ICS. As compared to its antiemetic effect after i.v. administration, a dissociation ratio of 272 (0.79/0.0029) was obtained. This is in line with the effects obtained in the shuttle box where the ratio between the lowest ED50 values of its central effects and antiemetic effects were found to be over 300, regardless of the route of administration (1). Thus with domperidone, CNS effects appear rather slowly and with high dose levels only, in contrast to the fast onset of its potent antiemetic activity. This again is in agreement with the in vivo finding in rats that homovanillic acid only slightly increased 6 to 8 hours following the
Table 3. Effects of domperidone and metoclopramide on apomorphine-induced emesis and stereotypy in dogs

<table>
<thead>
<tr>
<th>Dose (mg/kg i.v.)</th>
<th>Concentration (mg/ml)</th>
<th>Dilution from ampoules</th>
<th>Injected volume (ml)</th>
<th>Apo. emesis</th>
<th>Apo. stereotypy</th>
<th>Complete protection</th>
<th>Apo. emesis</th>
<th>Apo. stereotypy</th>
<th>Complete protection</th>
<th>Statistics (Finney, 1962)***</th>
<th>ED50 mg/Kg and fiducial limits</th>
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<td>1</td>
<td>0.010</td>
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<td>0</td>
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<td>U.L.: 0.090</td>
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* Apomorphine HCl 1.25 mg/Kg s.c. ** Finney, D.J. Probit analysis. Cambridge University Press, 1962.
excessively large subcutaneous dose of 10 mg/kg of domperidone. Metoclopramide at low doses induced a marked and immediate increase in HVA (14).

The lack of site-related effects on ICS is in line with the lack of site-specific effects on the EEG. Here again, domperidone slightly, and at high doses, 4 hr after i.v. administration increased slow frequency activity only and did not induced sleep-like patterns. Metoclopramide increased the potency of the EEG at all doses tested and shortly after injection.

The dissociation between the central and the antiemetic effects of domperidone and metoclopramide was evaluated in the same dogs treated with apomorphine by assessing simultaneously the antagonism of emesis and stereotypy. This experiment provided clear cut evidence that the central effects of domperidone appeared much later and were largely dissociated from its antiemetic effects (ratio 180), whereas metoclopramide induced central effects at doses nearly equal to its antiemetic dose (ratio 2.67).

Because of the large dissociation between the antiemetic and CNS effects obtained with domperidone in various sensitive tests, it can be concluded that domperidone as an antiemetic is virtually devoid of central effects, whereas the CNS effects of metoclopramide are concomitant with the antiemetic effects.

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