Aortic arterial systolic, diastolic and mean blood pressures (mmHg), heart rates (beats/min), ventricular systolic segmental shortenings (mm) and the QT intervals were continuously registered and automatically analysed every 15 minutes during the 5 hour observation period following Org 5222 administration. QTc (which reflects cardiac repolarisation time) was calculated according to Bazett's formula.

Dogs were tilted to the 90° upright position for periods of 30 seconds by lifting their forelimbs. Tilt responses refer to the maximum changes observed in aortic blood pressure and heart rate during the 30 second observation period and were assessed both 30 minutes and just before Org 5222 administration and then 15, 30, 60, 90, 120, 180, 240, and 300 minutes after administration.

Blood samples were taken just before drug administration and at 15, 30, 60, 90, 120, 240, 300, 360 minutes and at 21 hours after administration in each case just after tilt challenge. To plasma, prepared from the blood samples, internal standard (cis-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate (1:1); Org 5033) was added and Org 5222 and internal standard were isolated by extracting the alkalinized plasma with n-hexane. The Org 5222 concentration was determined by capillary gas chromatography (cGC) with NPD-detection.

Results

The hypotensive response to tilt was modestly and dose-dependently augmented by Org 5222, irrespective of the route of administration. However, for equivalent Org 5222 plasma levels, the accompanying tachycardia was always more marked after oral administration of Org 5222 than after sublingual administration (Table 1)

TABLE 1

Mean heart rate change due to tilt (corrected for placebo effects), calculated per concentration range (ng/ml) and for each of the two administration routes, oral (po) and sublingual (sl).

Org 5222 plasma concentration	Mean heart rate change per concentration range	
(ng/ml)	po	sl
0–3	5.7	4.6
3–10	21.3	0.6
10–30	21.1	18.3
30–100	47.8	14.9
100–300	52.8	8.9

Conclusions

Tachycardia accompanying orthostatic hypotension was more marked after oral than after sublingual administration of Org 5222. Direct haemodynamic and electrophysiological effects were also less marked after sublingual than after oral administration with regard to negative inotropy and QTc prolongation.

Moreover, dogs treated orally showed marked side effects such as excitation of long duration, whereas dogs treated sublingually showed only short excitation periods followed by long lasting sedation.

We claim:

1. A pharmaceutical composition comprising as a medicinally active compound: trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof; wherein the composition is a solid composition and disintegrates within 30 seconds in water at 37° C.

2. The pharmaceutical composition of claim **1**, wherein the composition further comprises a pharmaceutically acceptable water-soluble or water-dispersable carrier material.

3. The pharmaceutical composition of claim **2**, wherein the carrier material is partially hydrolysed gelatin.

4. A method for treating tension, excitation, anxiety, and psychotic and schizophrenic disorders, comprising administering sublingually or buccally an effective amount of a pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof.

5. The pharmaceutical composition of claim **1**, wherein the composition disintegrates within 10 seconds in water at 37° C.

6. The composition of claim **1**, further comprising one or more pharmaceutically acceptable auxiliaries selected from the group consisting of hydrolyzed dextran, dextrin, mannitol, algenates, polyvinyl alcohol, polyvinyl pyrrolidine and water soluble cellulose derivatives.

7. A pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof; and pharmaceutically acceptable auxiliaries, wherein the composition is made by the process of

a) providing an aqueous solution comprising said compound and a water soluble or water dispersable carrier material;

b) transferring the composition of a) into a mold;

c) freezing the composition in the mold; and

d) subliming the solvent by freeze-drying.

8. A pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate, mannitol, and gelatin.

9. The method of claim **4**, wherein the composition is a solid pharmaceutical composition which rapidly disintegrates in the mouth of a subject upon insertion into the buccal pouch or upon placement under the tongue.

10. The method of claim **4**, wherein the pharmaceutical composition further comprises pharmaceutically acceptable auxiliaries selected from the group consisting of hydrolyzed dextran, dextrin, mannitol, algenates, polyvinyl alcohol, polyvinyl pyrrolidine and water soluble cellulose derivatives.

11. The method of claim **10**, wherein the pharmaceutically acceptable auxiliary is partially hydrolyzed gelatin.

12. The method of claim **4** wherein the pharmaceutical composition comprises trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole maleate, mannitol, and gelatin.

13. A method for treating antihistamine and antiserotonin related diseases comprising administering sublingually or buccally an effective amount of a pharmaceutical composition comprising trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole or a pharmaceutically acceptable salt thereof.

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