metabolites are significantly enhanced in the presence of muscimol, suggesting that these compounds may not be benzodiazepine antagonists.

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(RO 15-1788 is: ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]-benzodrazepine-3-carboxylate.)

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Mianserin: is the intraperitoneal route of administration the best?

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A 1 h pretreatment with s.c. mianserin (0·5 mg kg^{-1}) markedly blunted the oedema of the rat paw induced by the subplantar injection of 5-HT (5 μg). In contrast, i.p. mianserin (same dose) failed to modify 5-HT-induced oedema. However, pretreatment with SKF-525-A (40 mg kg^{-1}) resulted in a profound potentiation of the action of i.p. mianserin, the effect of the combination of SKF-525-A and i.p. mianserin rivalling that of s.c. mianserin. It is concluded that i.p. mianserin is metabolized by the rat liver to compounds which possess a reduced propensity to block peripheral 5-HT receptors and that the i.p. route of administration is not to be recommended when mianserin is being studied as a 5-HT receptor antagonist in the rat.

The tetracyclic antidepressant mianserin is a potent 5-hydroxytryptamine (5-HT) receptor antagonist (Vargaftig et al 1971). In the course of studying this property of the drug it was observed that the ability of mianserin to block the resultant oedema of the rat paw following the subplantar injection of 5-HT was markedly dependent on its route of administration and it was decided to pursue this observation.

Method

Male Sprague-Dawley rats, 200–250 g, were used. The rear left paw received a subplantar injection (0·1 ml) of 5 μg of 5-HT creatinine sulphate. The contralateral paw received vehicle (0·9% NaCl). Paw thickness was measured 15 min after 5-HT injection using the apparatus described by Bonta & de Vos (1965). The recorded reading represented an approximate sevenfold amplification in the actual paw thickness. The dose of 5-HT used approximately doubled paw thickness. Mianserin hydrochloride was dissolved in distilled water and was injected either i.p. or s.c. 1 h before 5-HT. Doses of both mianserin and 5-HT refer to the free base. For each rat the thickness of both rear paws was measured and the difference in recorded values was expressed as percentage increase in thickness. Each result is the mean ± s.e.m. of at least six observations and statistical significance was determined using Student's *t*-test (two-tailed).

Results

The i.p. injection of mianserin, 0·5 mg kg^{-1}, was devoid of effect on the 5-HT-induced swelling of the rat paw (Table 1). Increasing the dose to 1 mg kg^{-1} resulted in a modest, statistically significant inhibition. In contrast, the s.c. injection of mianserin, 0·5 mg min^{-1}, markedly blunted the response to 5-HT. Hence, the response to mianserin, 0·5 mg kg^{-1}, is markedly dependent on the route of administration. The s.c. injection of 0·05 and 0·1 mg kg^{-1} of mianserin also significantly antagonized the 5-HT-induced oedema. The inability of mianserin, 0·5 mg kg^{-1} i.p., to attenuate the paw swelling evoked by 5-HT was reversed by a 1 h pretreatment with SKF-525-A, 40 mg kg^{-1} i.p., the inhibitory action of the combination rivalling that of mianserin, 0·5 mg kg^{-1} s.c.

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Table 1. Effect of mianserin pretreatment on 5-HT-induced oedema of the rat paw. Mianserin was injected either i.p. or s.c. 1 h before the subplantar injection of 5-HT (5 μg). Paw thickness was measured 15 min after 5-HT injection. SKF-525-A, 40 mg kg^{-1}, was injected i.p. 1 h before mianserin. Results are expressed as the percent increase in paw thickness relative to the contralateral vehicle-treated paw and are the mean ± s.e.m.

Treatment	Dose (mg kg^{-1})	Route	n	% Increase in paw thickness: 5-HT	5-HT + treatment
Mianserin	1	i.p.	6	68·0 ± 2·5	38·1 ± 8·2**
Mianserin	0·5	i.p.	18	72·4 ± 2·6	67·4 ± 3·7
SKF-525-A + mianserin	0·5	i.p.	12	80·3 ± 3·2	15·7 ± 3·0***
SKF-525-A	40	i.p.	12	80·3 ± 3·2	79·6 ± 3·2
Mianserin	0·5	s.c.	18	76·4 ± 2·6	18·4 ± 1·7***
Mianserin	0·1	s.c.	6	93·3 ± 4·7	39·8 ± 4·7***
Mianserin	0·05	s.c.	6	93·3 ± 4·7	66·4 ± 5·0*

* Differs from 5-HT, $P < 0·05$. ** Differs from 5-HT, $P < 0·01$. *** Differs from 5-HT, $P < 0·001$.

SKF-525-A alone was devoid of effect on paw thickness.

Discussion

The above observations clearly reveal that the ability of mianserin to block 5-HT-induced oedema of the rat paw is markedly dependent on its route of administration. The s.c. injection of mianserin was extremely effective in blocking the response to 5-HT, a significant inhibition being elicited by 0·05 mg kg^{-1}. It appears unlikely that the difference between the two routes of administration is due to the slower absorption of mianserin following s.c. administration since a 1 h pretreatment with i.p. mianserin is associated with a blockade of central α_2-adrenoceptors in the rat (Sugrue 1980). In the original studies of Vargaftig et al (1971), mianserin was injected either s.c. or orally and results of both this and that study investigating the effect of s.c. mianserin on 5-HT-induced rat paw oedema are in good agreement. In contrast, when mianserin is injected i.p. much larger doses of the drug are required to achieve a significant effect, i.e. 1 mg kg^{-1}. The marked difference between i.p. and s.c. mianserin suggested that the reduced effectiveness of i.p mianserin was due to the metabolism of the drug by the liver since compounds injected i.p. are primarily absorbed through the portal circulation and, therefore, must pass through the liver before reaching other organs (Lukas et al 1971). To test this hypothesis, rats were pretreated with SKF-525-A, an inhibitor of drug metabolism by liver microsomes (Anders 1971). SKF-5235-A, 40 mg kg^{-1} i.p., is devoid of effect on 5-HT-induced oedema. However, it dramatically potentiated the effect of mianserin, 0·5 mg kg^{-1} i.p., and it is to be noted that the effect of the combination was comparable to the effect of the same dose of mianserin injected s.c. The metabolism of mianserin in rats following oral administration has recently been reported (De Jongh et al 1981). The drug is principally metabolized to 8-hydroxy compounds and to a lesser extent to demethylated metabolites. The major metabolites in rat are 8-hydroxymianserin and 8-hydroxydesmethylmianserin. 8-Hydroxymianserin retains the ability of mianserin to block α_2-adrenoceptors (Nickolson et al 1982). However, the ability of 8-hydroxymianserin to antagonize 5-HT-induced bronchoconstriction in guinea-pigs is markedly less than that of mianserin (Pinder & Van Delft 1983). Hence it appears that the i.p. injection of mianserin to rats is associated with the rapid metabolism of the drug by the liver to metabolites which possess a greatly reduced ability to block peripheral 5-HT receptors.

In summary, the results of this study indicate that the route of administration of mianserin can have an important bearing on the interpretation of the observed results. Moreover, it is apparent that the i.p. route should not be used when mianserin is being studied in rats as a 5-HT receptor antagonist.

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