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Droperidol concentrations at onset of catalepsy in rats

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Droperidol infused at 0.086, 0.095, 0.18 or 0.32 mg/min/kg induced catalepsy in rats at ~3 mg/kg and at serum concentrations clinically observed in patients. Serum and brain concentrations at onset of catalepsy were dependent on the infusion rate and did not reflect concentrations at its site of catalepsy especially at rapid infusion rates.

Droperidol is used as anaesthesia premedication, induction and for neuroleptanaesthesia (Edmonds-Seal and Prys-Roberts 1970). Catalepsy and akinesia in rats and Parkinson-like symptoms in humans result from dopamine receptor blockade by droperidol and related neuroleptics (Janssen et al. 1965); catalepsy is closely related with its extrapyramidal side effects in patients. Droperidol (3–12 mg/kg) induces catalepsy in rats 90 min after i.p. injection (Freye and Kuschinsky 1976). A close relationship exists between droperidol induced catalepsy and increased turnover of striatal dopamine as evidenced by increase in homovanillic acid, a dopamine metabolite (Freye and Kuschinsky 1976). However, no data is available on droperidol concentrations in serum or the CNS at onset of catalepsy. The present study characterised droperidol induced catalepsy in rats. Specifically serum and brain droperidol concentrations were quantified at onset of catalepsy as a function of droperidol input rate.

Droperidol induced catalepsy in rats in 12 to 28 min when infused i.v. between 0.32 and 0.086 mg/min/kg (Table). Droperidol dose ($r^2 = 0.913$, $P < 0.001$), serum and brain concentrations (Fig.) all increased linearly as droperidol infusion rate was increased. There was a concentration 'overshoot' in both serum and brain when droperidol was infused rapidly to elicit catalepsy in rats. Equilibrium with respect to brain concentrations was noted at the two slower rates of infusion but with serum this was noted with the two intermediate rates. The serum results reflect a temporal dysequilibrium at the fastest input rate and possible contribution from a droperidol metabolite (Soudijn et al. 1974) to the catalepsy would be consistent with the lower droperidol serum concentration at the slowest input rate where more metabolite would be generated. Thus while the droperidol concentration in brain (and serum) did not reflect true biophase (catalepsy effect site) concentration due to the temporal dysequilibrium between serum and the CNS (and perhaps active metabolite generation/accumulation), brain concentrations at the two slower infusion rates were the same, indicative of equilibration with the effect site at slow rates of input (Table). The brain to serum droperidol concentration ratios varied from just below unity to 1.6 (Table).

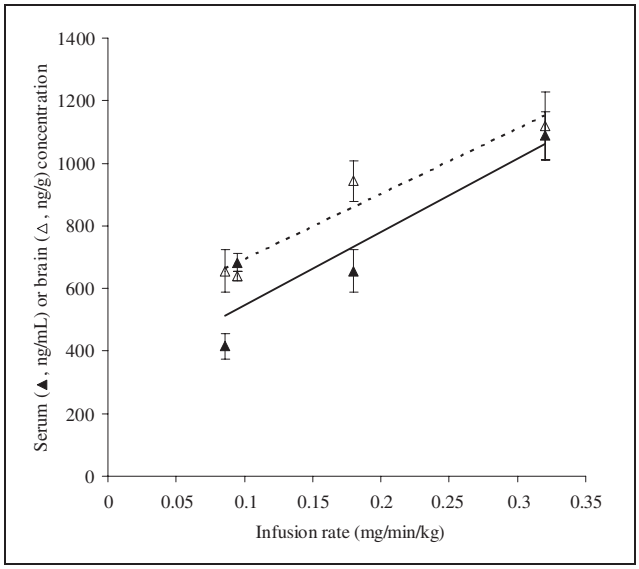

Fig.: Infusion rate dependency of droperidol serum ($r^2 = 0.944$) and brain ($r^2 = 0.966$) concentrations at onset of catalepsy

In summary droperidol induced catalepsy in rats at a dose of approximately 3 mg/kg and at serum concentrations that are encountered clinically (1000–3000 ng/mL) in patients (Fischler et al. 1986). However, serum and brain concentrations at onset of catalepsy were dependent on the droperidol infusion rate and did not reflect concentrations at its site of catalepsy especially if infusion rates were rapid.

Experimental

Prior to the catalepsy study droperidol pharmacokinetics were determined for infusion rate calculation in six rats dosed with droperidol (3 mg/kg) as an i.v. bolus followed by sequential blood sampling for 180 min. In another preliminary study, using nine rats, an i.v. bolus dose of 3 mg/kg droperidol was noted to induce catalepsy. This droperidol dose was therefore administered to four groups of eight rats as i.v. infusion via the jugular vein. Infusion rates were chosen to induce catalepsy within a time that represented a fraction of the elimination half-life of droperidol in rats

Table: Droperidol doses and concentrations at onset of catalepsy

Parameter	Droperidol infusion rate (mg/min/kg)				P_{ANOVA}
	0.086	0.095	0.18	0.32	
Infusion time (min)	27.7 ± 1.2	23.7 ± 1.5	19.4 ± 0.6	11.5 ± 0.4	<0.001
Dose (mg/kg)	2.4 ± 0.1	2.3 ± 0.1	3.4 ± 0.1[a]	3.8 ± 0.1[a]	<0.001
Serum conc. (ng/mL)	416 ± 40[a]	683 ± 28	655 ± 68	1088 ± 76[a]	<0.001
Brain conc. (ng/g)	655 ± 68	640 ± 15	944 ± 65[b]	1120 ± 109[b]	<0.001
Ratio Brain/Serum	1.58 ± 0.08[c]	0.94 ± 0.02	1.56 ± 0.18[c]	1.04 ± 0.10	<0.001

Mean ± SEM, n = 8 each group,
[a] $P < 0.05$ compared with other rates (Fishers LSD test), [b] $P < 0.05$ compared with two slower (0.086 & 0.095) rates. [c] $P < 0.05$ compared with other two rates

(~25 min from the pharmacokinetic study). Each rat was placed with both its forepaw on the edge of a plastic observation box, onset of catalepsy was noted if the rat remained in this position for 45 s, rats not receiving droperidol scurried away within a few seconds. A similar catalepsy endpoint has been used previously (Freye and Kuschinsky 1976). The infusion was stopped immediately, the rats quickly anaesthetised with halothane and blood (abdominal aorta) and then brain was obtained following decapitation. Droperidol was assayed in serum and brain using reversed phase liquid chromatography (Guichard et al. 1993) but with a different internal standard (diazepam). This involved solid phase extraction and UV detection at 245 nm. Droperidol and diazepam retention times were 12.8 and 8.4 min. Recovery from brain and serum was $75 \pm 4\%$, intra- and inter-day assay variability was 2.0–6.8% and 6.2–12.3% and the limit of quantitation was 25 ng/mL. Droperidol doses and concentrations as a function of input rate were compared using ANOVA and post hoc Fishers LSD test, $P < 0.05$ was considered significant.

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Inhibitory activity of indolin-2-one derivatives on compound 48/80-induced histamine release from mast cells

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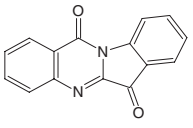
Four alkaloids, previously identified in *Isatis* species, were tested for their inhibitory effect on histamine release. Whereas tryptanthrin, indirubin and deoxyvasicinone did not inhibit histamine release, the effect of indolin-2-one exceeded that of the mast cell stabilizing drug disodium chromoglycate.

Isatis tinctoria L. (woad, family Brassicaceae) is an old indigo dye and anti-inflammatory medicinal plant (Hurry 1930). A broad-based pharmacological profiling in a panel of cell-based and mechanism-based assays involving over 20 inflammation-related targets showed that a lipophilic extract from woad leaves significantly inhibited cyclooxygenase-2, 5-lipoxygenase, inducible NO synthase, leucocytic elastase, and histamine and serotonine release from stimulated mast cells (Hamburger 2002). We identified the alkaloid tryptanthrin (**1**) as the COX-2 inhibitory principle in woad (Danz et al. 2001). The compound also strongly inhibited LTB_4 release from human granulocytes and expression of inducible NO synthase (Danz et al. 2002; Ishihara et al. 2000). *Isatis* extracts and, to a lesser extent, **1** alone, showed anti-inflammatory activity in carageenan-induced paw oedema and in TPA-induced mouse ear oedema (Recio et al. 2002), and a clinical pilot study confirmed the anti-inflammatory effect of topical application in clinically relevant skin irritation models (Heinemann et al. 2004).

In the search for woad constituents responsible for the inhibitory effect on histamine release, we adapted existing assay protocols with compound 48/80 stimulated rat mast



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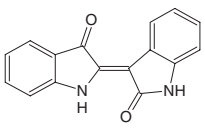

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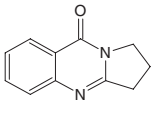

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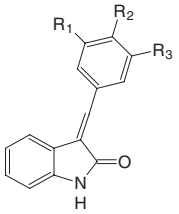

	R_1	R_2	R_3
4	- OCH_3	- OH	- OCH_3
5	- H	- OH	- H
6	- $C(CH_3)_3$	- OH	- $C(CH_3)_3$
7	- H	- $CH(CH_3)_2$	- H
8	- H	- H	- H
9	- $C(CH_3)_3$	- OCH_3	- H