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REFERENCES

Bennett, A., Eley, K. G., Scholes, G. B. (1968) Br. J. Pharmacol. 34: 630–638

Grbović, L., Radmanović, B. Ž. (1978) Arch. Int. Pharmacodyn. Ther. 235: 230–237

Grbović, L., Radmanović, B. Ž. (1979) Neuropharmacol. 18: 667–671

Grbović, L., Radmanović, B. Ž. (1981) Arch. Int. Physiol. Biochem. 89: 379–383

Gustaffson, L. (1975) Acta Physiol. Scand. 95: 26–31

Hanh, R., Patil, P. N. (1972) Br. J. Pharmacol. 44: 527–532

Hanh, R., Patil, P. N. (1974) Eur. J. Pharmacol. 25: 279–284

Harry, J. D. (1968) Br. J. Pharmacol. 33: 213P

Litchfield, J. T., Wilcoxon, F. (1949) J. Pharmacol. Exp. Ther. 96: 99–113

Poddibuik, Z. M., Kleinrok, Z. A. (1976) Psychopharmacol. 50: 95–101

Radmanović, B. Ž., Grvović, L. (1979) Yugosl. Physiol. Pharmacol. Acta 15: 189–195

Radmanović, B. Ž. (1980) Farmakologia i Toksikologia (Moskva) 6: 717–720

Vane, J. R. (1972) Hospital Practice March, 61–67

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Plasma concentrations of trazodone and 1-(3-chlorophenyl)piperazine in man after a single oral dose of trazodone

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Trazodone, a non-tricyclic antidepressant agent (for a review see Brogden et al 1981) is metabolized to form, among other metabolites (Yamato et al 1974, 1976; Baiocchi et al 1974; Jauch et al 1976) 1(3-chlorophenyl)piperazine (CPP) (Melzacka et al 1979; Caccia et al 1981 a,b) which has several pharmacological activities; it is anorectic (Samanin et al 1979) analgesic (Rochat et al 1982) and anti-withdrawal in morphine-tolerant rats (Cervo et al 1981). Furthermore CPP shows effects on the central 5-hydroxytryptaminergic system compatible with agonistic activity on 5-HT postsynaptic receptors (Samanin et al 1979; Rokosz-Pelc et al 1980). CPP was also found in rats after oral administration of trazodone. It accumulates in the brain at concentrations comparable to those found after the administration of pharmacologically and biochemically effective doses of CPP (Caccia et al 1981b; Cervo et al 1981). Independent studies by Maj's group indicated that trazodone has biphasic action on the central 5-HT-ergic mechanisms; at lower doses the drug displays antagonist properties and at high doses an agonistic effect predominates (Maj et al 1979). The latter effect has been attributed to the formation of CPP (Maj et al 1980).

All these findings suggest that CPP contributes to some extent to the therapeutic effect of trazodone in depressed patients. To support this hypothesis it must first be demonstrated that CPP is actually formed in man treated with trazodone.

Methods

Four healthy volunteers, from 21 to 30 years and from 49 to 80 kg, participated in a study. After an overnight fast, subjects ingested a single dose (150 mg) of trazodone hydrochloride and blood samples were drawn over 10 h. Blood samples were centrifuged to separate plasma and stored at −20 °C. Urine was collected for 24 h dosing and hydrolysed with β-glucoronidase-arylsulphatase. Male CD-COBS rats, ca 200 g (Charles River, Italy), were orally dosed with 25 mg kg^{-1} of trazodone hydrochloride. Concentrations of trazodone and CPP in plasma, brain and urine (5 ml) were determined by gas liquid chromatography as previously described (Caccia et al 1981a).

Results

Small amounts of trazodone were found in the 24 h urine of volunteers (0·5 ± 0·3% of the administered dose) in agreement with previous reports (Catanese & Lisciani 1970; Yamato et al 1976) that the drug is almost completely eliminated from the body by biotransformation. CPP was present in the urine of all four subjects as a minor metabolite amounting to only 0·15 ± 0·05% of the trazodone administered dose. Specificity of the

Table 1. Mean plasma concentrations of trazodone (Tz) and 1-(3-chlorophenyl)piperazine (CPP) after a single 150 mg dose of trazodone hydrochloride to 4 human subjects. * Mean 3 subjects.

Time (h)	Plasma concentrations (nmol ml^{-1} ± s.e.m.)	
	Tz	CPP
1	4·66 ± 0·46	0·03 ± 0·01*
2	5·24 ± 0·38	0·05 ± 0·02
4	3·21 ± 0·58	0·06 ± 0·02
6	2·19 ± 0·30	0·05 ± 0·02
8	1·52 ± 0·08	0·04 ± 0·01*
10	1·03 ± 0·17	0·03 ± 0·01*

* Correspondence.

Table 2. Peak concentrations C_{max}, half-lives ($t_{1/2}$) and area under the curve (AUC) of trazodone (Tz) and 1-(3-chlorophenyl)piperazine (mCPP) in man and rat.

Species	Dose	Compartment	C_{max} (nmol ml^{-1} ± s.e.m.)*		$t_{1/2}$ (h ± s.e.m.)		AUC(nmol ml^{-1} h^{-1} ± s.e.m.)	
			Tz	CPP	Tz	CPP	Tz	CPP**
Man (n=4)	150 mg orally	Plasma	5·52 ± 0·41	0·06 ± 0·02	3·50 ± 0·20	4·20 ± 0·20**	32·80 ± 2·68	0·67 ± 0·23**
Rat (n=4)	25 mg kg^{-1} orally	Plasma	3·77 ± 0·53	0·22 ± 0·03	0·83***	1·62***	1·79***	0·85***
		Brain	4·03 ± 0.67	5.95 ± 0·49	1·28***	1·38***	9.10***	22·23***

* Observed values. ** Mean of only 3 subjects. *** Calculated according to the mean of 4 rats.
Plasma and brain AUC from zero to infinity were calculated using the trapeizoidal rule.

analysis was established by combined gas chromatography with mass spectrometry (g.l.c.–m.s.) which confirmed that the pathways of trazodone metabolism in man as in rat, include the formation of CPP. Furthermore the kinetic profile of trazodone and its active metabolite in the plasma of the volunteers was followed and compared with findings previously observed in rat plasma and brain after a pharmacologically active dose of trazodone (Caccia et al 1981a). Table 1 reports the mean plasma concentrations of trazodone and mCPP at different times after an oral dose of 150 mg trazodone hydrochloride. The drug was rapidly absorbed, reaching peak concentrations (C_{max}) of 5·52 ± 0·41 nmol ml^{-1} (about 2 μg ml^{-1}) generally within 2 h. The apparent half-life ($C_{1/2}$) of trazodone, calculated assuming the one compartment open model approximation, was 3.50 ± 0·20 h (Table 2). Similar results have been obtained in man by others (Catanese & Lisciani 1970; Yamato et al 1976; Brogden et al 1981).

The metabolite CPP reached C_{max} (0·06 nmol ml^{-1} corresponding to 0·01 μg ml^{-1}) within 2–4 h, amounting to about 1% of the parent drug plasma concentrations. The plasma $t_{1/2}$ of CPP was slightly longer (4·20 ± 0·20 h) than that of the parent drug. In one subject the plasma concentrations of mCPP were too low to be determined.

In the rat, despite the fact that the dose was 10 times higher, the C_{max} of trazodone (3·77 ± 0·53 nmol ml^{-1}, at 5 min) was lower while the C_{max} of CPP (0·22 ± 0·03 nmol ml^{-1}, at 2 h) was nearly four times higher than in man. However due to the different apparent plasma $t_{1/2}$ the area describing the concentrations in relation to time (AUC) was lower for trazodone and similar for CPP in rats and man.

If it is assumed that the ratio of brain to plasma C_{max} is similar (about 27) in rats and man it can be concluded that brain concentrations of CPP in the brain of man may approach biochemically effective levels. Whether in patients mCPP contributes to the overall effects of trazodone remains a matter of speculation.

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REFERENCES

Baiocchi, L., Frigerio, A., Giannangeli, M., Palazzo, G. (1974) Arzneim. forsch. 24: 1699–1706

Brogden, R. N., Heel, R. C., Speight, T. M., Avery, G. S. (1981) Drugs 21: 401–429

Caccia, S., Ballabio, M., Fanelli, R., Guiso, G., Zanini, M. C. (1981a) J. Chromatogr. 210: 311–318

Caccia, S., Ballabio, M., Samanin, R., Zanini, M. G., Garattini, S. (1981b) J. Pharm. Pharmacol. 33: 477–479

Catanese, B., Lisciani, R. (1970) Bol. Chim. Farm. 109: 369–373

Cervo, L., Ballabio, M., Caccia, S., Samanin, R. (1981) J. Pharm. Pharmacol. 33: 813–814

Jauch, R., Kopitar, Z., Prox, A., Zimmer, A. (1976) Arzeneim. forsch. 26: 2084–2089

Maj, J., Baran, L., Bigajska, K., Rawłów, A. (1980) in: Gershon, S., Rickels, K., Silvestrini, B. (eds) Trazodone: A new Broad-Spectrum Antidepressant. Excerpta Medica, Amsterdam, pp 34–38

Maj, J., Palider, W., Rawłów, A. (1979) J. Neural. Transm. 44: 237–248

Melzacka, M., Boksa, J., Maj, J. (1979) J. Pharm. Pharmacol. 31: 855–857

Rochat, C., Cervo, L., Romandini, S., Samanin, R. (1982) Ibid. 34: 325–327

Rokosz-Pelc, A., Antkiewicz-Michaluk, L., Vetulani, J. (1980) J. Pharm. Pharmacol. 32: 220–222

Samanin, R., Mennini, T., Ferraris, A., Bendotti, C., Borsini, F., Garattini, S. (1979) Naunyn-Schmiedeberg's Arch. Pharmacol. 308: 159–163

Yamato, C., Takahashi, T., Fujita, T. (1974) Xenobiotica 4: 313–326

Yamato, C., Takahashi, T., Fujita, T. (1976) Ibid. 6: 295–306