Rimm, A. A., Hartz, A. J., Kalbfleisch, J. H., Anderson, A. J., Hoffman, R. G. (1980) in: Basic biostatistics in medicine and epidemiology, Appleton-Century-Crofts, New York, pp 268

Sparber, S. B., Meyer, D. R. (1978) Pharmacol. Biochem. Behav. 9: 319–325

Tanaka, T., Starke, K. (1979) Naunyn-Schmiedeberg's Arch. Pharmacol. 309: 207–215

Tseng, L. F., Loh, H. H., Wei, E. T. (1975) Eur. J. Pharmacol. 30: 93–99

Vetulani, J., Bednarczyk, B. (1977) J. Pharm. Pharmacol. 29: 567–569

J. Pharm. Pharmacol. 1981, 33: 399–400
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Effect of carnitine on heart alterations caused by tricyclic antidepressants

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Overdoses of tricyclic antidepressant drugs (TAD) may cause a number of adverse reactions among which cardiac arrhythmias are fairly frequent (Barnes et al 1968; Coull et al 1970; Jefferson 1975). Pyridostigmine β-adrenoceptor blocking agents and lignocaine are not completely satisfactory in the management of these disturbances (Torchiana et al 1972).

The observation that carnitine, a factor involved in the transfer of fatty acids across membrane (Fritz & Marquis 1965), beneficially influences some cardiac functions (Folts et al 1976; Vick et al 1976; Brook et al 1977) suggested we investigate whether this compound might in some way counteract the cardiac damage induced by TAD.

Materials and methods

Male New Zealand white rabbits, 2·5–3 kg, were anaesthetized with ethylurethane 1·2 g kg^{-1}. Nortriptyline hydrochloride (0·18 mg kg^{-1} min^{-1} (kindly supplied by Recordati, Milan, Italy) and (±)-carnitine hydrochloride (10 mg kg^{-1} min^{-1}, kindly supplied by SigmaTau, Pomezia, Italy), were infused into the marginal veins of respectively the right and the left ears. Each infusion lasted 40 min. When both compounds were given, carnitine infusion began 20 min before that of nortriptyline. Blood was withdrawn from the artery of the left ear at the beginning of the experiment, before starting nortryptiline infusion. E.c.g.s were traced by a Grass electrocardiograph. Standard limb connections were made with subcutaneous needle electrodes, lead II being mainly used for quantifying PQ and QRS intervals, which were measured with the help of a magnifying loop. At the end of the infusion, plasma and heart were collected and frozen. Nortriptyline was determined according to Bailey & Jatlow (1976) and (±)-carnitine according to Seccombe et al (1978). Statistical differences were evaluated by two-way analysis of variance and Tukey's test.

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Results and conclusions

Nortriptyline infusion caused a number of e.c.g. alterations. As shown in Table 1, PQ and QRS intervals progressively widened; at the end of infusion the PQ wave was virtually unmeasurable, and voltage waves were increased by about 100% in all the rabbits given nortryptiline. Episodes of ventricular tachycardia and bundle branch block were noted in 5 out of 8 rabbits.

Carnitine infusion itself did not result in modification of the e.c.g., but it delayed the widening of the PQ and QRS intervals caused by nortriptyline, and PQ intervals

Table 1. Effect of carnitine on e.c.g. abnormalities caused by nortriptyline.

	E.c.g. parameters					
	PQ ms ± s.e.			QRS ms ± s.e.		
Time (min)	Car.	Nort.	Car. + Nort.	Car.	Nort.	Car. + Nort.
Baseline	68 ± 2·0	59·8 ± 3·5	61·3 ± 1·9	28 ± 1	34·4 ± 1·1	33·5 ± 0·5
25	73 ± 1·5	63·6 ± 3·5	62·0 ± 1·8	28 ± 0·6	37·4 ± 1·2	34·8 ± 0·7
30	—	66 ± 3·5	62·0 ± 1·8	—	41·3 ± 1·3	36·7 ± 1·2
35	—	69·8 ± 2·8	63·6 ± 2·1	—	43·7 ± 1·3	38·2 ± 1·4
40	68·5 ± 2·0	78·2 ± 5·2	64·3 ± 1·8	29 ± 1	46·1 ± 1·6	41·2 ± 1·2
50	—	n.d.	66·1 ± 2·0	—	51·6 ± 1·9	41·5 ± 1·8
50	68·5 ± 2·0	n.d.	67·7 ± 2·2	28 ± 1·2	54·7 ± 1·9	45·2 ± 1·8

Car. = (±)-Carnitine HCl = 10 mg kg^{-1} min^{-1} × 40 min.
Nort. = Nortriptyline HCl = 0·18 mg kg^{-1} min^{-1} × 40 min.
Means of 8 rabbits ± standard error.

Table 3. Plasma and heart (−)-carnitine concentrations after infusion of (±)-carnitine and nortriptyline.

Treatment		(−)-Carnitine nmol litre^{-1} or g^{-1} ± s.e.					
		Plasma			Heart		
Car.	Nort.	Total	Free	Esterified	Total	Free	Esterified
−	−	38 ± 5	22 ± 4	16 ± 3	1188 ± 173	648 ± 87	542 ± 94
−	+	43 ± 8	30 ± 9	13 ± 5	1010 ± 135	672 ± 77	338 ± 89
+	−	1201 ± 181	1136 ± 191	64 ± 14	1157 ± 65	735 ± 36	421 ± 35
+	+	1597 ± 220	1242 ± 86	326 ± 92	1508 ± 66	1068 ± 18	440 ± 89

Car. = (±)-carnitine HCl = 10 mg kg^{-1} min^{-1} × 40 min.
Nort. = nortripytline HCl = 0·18 mg kg^{-1} min^{-1} × 40 min.
Means ± s.e. of 8 rabbits per group.

Table 2. Plasma and heart nortriptyline concentrations in rabbits after infusion of nortriptyline and nortriptyline + (±)-carnitine.

Treatment		Nortriptyline concn		
Car	Nort.	Plasma μg ml^{-1} ± s.e.	Heart μg g^{-1} ± s.e.	Heart/plasma
−	+	1·98 ± 0·43	28·5 ± 4·0	15·3 ± 1·5
+	+	1·64 ± 0·17	30·9 ± 5·0	19·9 ± 4·4

Car = (±)-carnitine HCl = 10 mg kg^{-1} min^{-1} × 40 min.
Nort = nortriptyline HCl = 0·18 mg kg^{-1} min^{-1} × 40 min.

were still measurable 20 min after stopping carnitine infusion. Carnitine infusion partially prevented the wave voltage increases in 5 out of 8 rabbits (50% increase), but ventricular tachycardia and bundle branch block occurred in two out of 8 rabbits.

As the onset of cardiac disturbances during nortriptyline infusion has been shown to be related to the drug concentration reached in the heart (Dejana et al 1979), we investigated whether carnitine infusion competed with nortriptyline uptake in the heart. The Results, in Table 2, show that this was not so: nortriptyline concentrations in plasma and heart were not affected by carnitine infusion.

On the other hand the observed effect could not be attributed to concentrations of carnitine in the heart, because (see Table 3) nortriptyline did not deplete carnitine in the heart and carnitine infusion did not raise it.

These observations suggest that carnitine provides some degree of protection against nortriptyline cardiotoxicity, but the mechanism requires further investigation.

REFERENCES

Bailey, D. M., Jatlow P. I. (1976) Clin. Chem. 22: 777–781

Barnes, R. J., Kong, S. M., Wu, B. W. Y. (1968) Br. Med J. 3: 222–223

Brook, S., Goldberg, L., Holland, R., Klein, M., Sanzari, N., De Felice, S. (1977) J. Clin. Pharmacol. 17: 561–568

Coull, D. C., Crooks J., Dingwall-Fordyce, I., Scott, A. M., Weir, R. D. (1970) Lancet 2: 590–591

Dejana, E., Latini, R., Preziati, L., Quintana, A., Bonaccorsi, A. (1979) J. Pharmacol. Method 2: 241–250

Folts, J. B., Shug, A. S., Koke, J. R., Bittar, N. (1976) Clin. Res 24: 217A

Fritz, I. B., Marquis, N. R. (1965) Proc. Nat. Acad. Sci., USA 54: 1226–1233

Jefferson, J. W. (1975) Psychosom. Med. 37: 160–179

Seccombe, D. W., Hahn, P., Novak, M. (1978) Biochim. Biophys. Acta 528: 483–489

Torchiana, M. L., Wenger, H. C., Lagerquist, B., Morgan, G. M., Stone, C. A. (1972) Toxicol. Appl. Pharmacol. 21: 383–389

Vick, J. A., De Felice, S., Sanzari, N., Klein, M. (1976) Physiologist 19: 111