Delayed Ethanol Elimination in Rats after Application of Cefamandole or Cefoperazone

Klaus G. Römer[1], Klaus J. Freundt[1,2], Oscar Torres Alanis[1] and Graciela Garcia de Torres[1]

Received: December 29, 1983; accepted: May 1, 1984.

Abstract: Adult female Sprague-Dawley rats received ethanol (2 g/kg b.w., i.p.) 18 hours after pretreatment with the betalactam-antibiotics cefamandole (CMD) or cefoperazone (CPZ) (1 mmol/kg b.w. each, i.p.). The blood ethanol concentrations, determined repeatedly within 4 hours by head space GC, were increasingly elevated after CMD or CPZ up to twice the respective control values. The possible clinical and forensic significance of these findings for the therapeutic use of CMD or CPZ is pointed out.

Betalactam antibiotics containing a 1-methyltetrazole-5-thiol group may elicit an alcohol intolerance in man with facial flushing, tachycardia and nausea (disulfiram-like reaction) (1, 2, 3, 4). A possible reason could be an enhancement of the blood acetaldehyde concentration (5, 6, 7) caused by an inhibition of acetaldehyde dehydrogenase (7) which was found in experiments with rats. In addition we report here a retardation in blood ethanol decline in rats pretreated with the betalactam antibiotics cefamandole (CMD) or cefoperazone (CPZ) which contain the 1-methyltetrazole-5-thiol group.

Materials and Methods

Female SPF Sprague-Dawley rats (weighing 200–220 g) were obtained from the Central Breeding Station of the University of Heidelberg, FRG. The animals were housed in Macrolon cages (53 x 32 x 19 cm, 6 rats per cage) under standardized conditions (temperature 22°C, relative humidity approximately 50 %; 12-hour neon lighting for simulation of light-dark cycles; standard diet from Altromin, Lage, FRG, and tap water *ad libitum*). The following materials were used: cefamandole nafate, Mandokef® (Ely Lilly, Giessen, FRG); cefoperazone sodium, Cefobis® (Pfizer, Karlsruhe, FRG); ethanol (Merck, Darmstadt, FRG). The rats received 1 mmol/kg b.w. of CMD (n = 4) or CPZ (n = 4) in physiological (0.9 %, w/v) saline (2 ml/kg) i.p.; eighteen hours thereafter the rats were administered i.p. doses of 2 g/kg ethanol in 5 ml physiological saline/kg. Physiological saline (2 ml/kg) was given i.p. 18 hours before administration of ethanol (2 g/kg in 5 ml physiological saline/kg i.p.) to the controls (n = 24). Blood (0.02 ml) was repeatedly collected after ethanol dosing (10, 20, 40, 60, 120, 180, 240 min) from the retro-orbital plexus using heparinized disposable pipets. Ethanol was determined in blood by gas chromatography using a head-space method as described elsewhere (8). Dunnett's test (9) was used to determine any significant difference of the values of treated groups in comparison with the respective values of the controls. Changes were regarded as significant, if the p-values were less than 0.01.

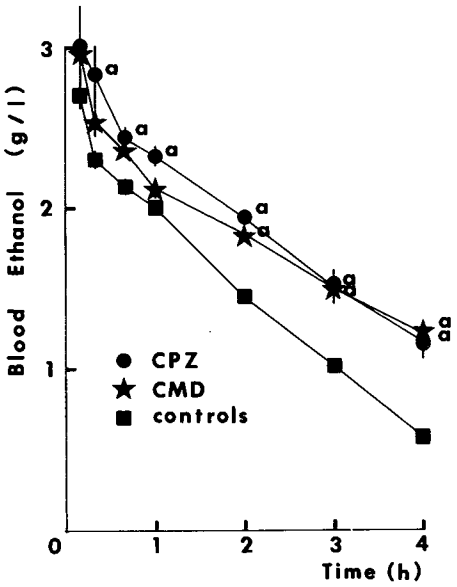

Fig. 1 Ethanol concentrations (mean ± SEM, determined from the individual values obtained) in the blood of rats. The significantly higher blood ethanol concentrations in the treated groups in comparison with the respective control groups are indexed (a) [Dunnett's test ($p < 0.01$)].

Table I. Increase of Blood Ethanol Concentrations in % (Related to the Respective Controls, Calculated from the Mean Values Given in Fig. 1) after Pretreatment with CMD or CPZ.

min	increase (%)	
	CMD	CPZ
10	10	12
20	10	23
40	10	14
60	6	16
120	27	34
180	47	48
240	110	102

Results and Discussion

The ethanol elimination from the blood of rats which had been pretreated with 1 mmol/kg b.w. CMD or CPZ 18 hours before ethanol dosing was markedly retarded, and the ethanol concentrations were significantly elevated over the respective controls (Fig. 1) until twice the control values were reached within 4 hours (Table I). The elevated blood alcohol concentrations measured in this study after CMD or CPZ in rats were also observed as an effect of latamoxef (7) which, similar to CMD and CPZ, also contains a 1-methyltetrazole-5-thiol group. The dose level of the cephalosporines was chosen at 1 mmol/kg, because in previous studies (8) a 10-fold lower dose had no effect on the kinetics of ethanol elimination.

The retardation of the alcohol elimination may not occur directly by an inhibition of alcohol dehydrogenase (ADH), since neither CMD nor CPZ inhibit rat hepatic ADH *in vitro* even in high doses (10), but rather indirectly by mass action of the accumulated acetaldehyde as a result of an inhibition of aldehyde dehydrogenase (ALDH). The

[1] Institute of Pharmacology and Toxicology, Faculty of Clinical Medicine Mannheim, University of Heidelberg, Maybachstr. 14–16, D-6800 Mannheim

[2] Correspondence to be addressed to Prof. Dr. K. J. Freundt, Institute of Pharmacology and Toxicology, Faculty of Clinical Medicine Mannheim, University of Heidelberg, Maybachstraße 14–16, D-6800 Mannheim

following *in vitro* findings suggest that the inhibition of ALDH is mediated by metabolites of the cephalosporines, rather than the parent drugs themselves. Rat liver ALDH was inhibited by latamoxef – which just like CMD or CPZ possesses a 1-methyltetrazole-5-thiol group and is structurally closely related to these two compounds – only if rat liver microsomes were added to the *in vitro*-reaction mixture at least 20 min earlier (11); thus, metabolites of latamoxef could be formed by oxidation. However, even maximal concentrations of CMD or CPZ did not inhibit the ALDH from rat liver *in vitro* without microsomes present (12). These observations suggest that so far unidentified metabolites of CMD and CPZ inhibit ALDH. Consequently, CMD and CPZ would act as indirect inhibitors of ethanol degradation by causing acetaldehyde accumulation, which affects ethanol elimination according to the law of mass action.

While recognizing that results from animal experiments cannot be transposed without restriction to the human situation, and taking into account the higher turnover of ethanol in rats compared with humans, the present finding suggests that after treatment with CMD or CPZ alcohol consumption may lead to increased ethanol blood levels of longer persistence. Under these circumstances an enhanced and prolonged effect of ethanol on the human organism has to be taken into account which may bear clinical or forensic significance. Further investigations to verify the present observations in human subjects are recommended.

References

(1) Drummer, S., Hauser, W. E., Remington, J. S. (1980) N. Engl. J. Med. 303, 1417–1418.
(2) McMahon, F. G. (1980) J. Am. Med. Ass. 243, 2397.
(3) Portier, H., Chalopin, J. M., Freysz, M., Tanter, Y. (1980) Lancet 2, 263.
(4) Reeves, D. S., Davies, A. J. (1980) Lancet 2, 540.
(5) Buening, M. K., Wold, J. S., Israel, K. S., Kammer, R. B. (1981) J. Am. Med. Ass. 245, 2027–2028.
(6) Yanagihara, M., Okada, K., Nozaki, M., Tsurumi, K., Fujimura, H. (1982) Folia Pharmacol. Japon. 79, 551–560.
(7) Yamanaka, Y., Yamamoto, T., Egashira, T. (1983) Jpn. J. Pharmacol. 33, 717–723.
(8) Römer, K. G., Torres Alanis, O., Garcia de Torres, G., Freundt, K. J. (1983) Pharmacol. Res. Commun. 15, 631–640.
(9) Tallarida, R. J., Murray, R. B. (eds.) (1981) Manual of Pharmacologic Calculations with Computer Programs, Springer Verlag, Berlin, Heidelberg, New York, 55–57.
(10) Schreiner, E., Christmann-Kleiss, U., Freundt, K. J. (1983) Naunyn-Schmiedeberg's Arch. Pharmacol. 322, Suppl., No. 464.
(11) Schreiner, E., Freundt, K. J., unpublished results.
(12) Schreiner, E., Christmann-Kleiss, U., Freundt, K. J. (1983) Naunyn-Schmiedeberg's Arch. Pharmacol. 324, Suppl., No. 332.